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**Utility and Safety of Invasive (Fractional Flow Reserve) and Non-Invasive (Cardiac
Magnetic Resonance Imaging) Diagnostic Test in Patients with NSTEMI**

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A Thesis Submitted for the Degree of Doctor of Medicine in the Faculty of Medicine of the
University of Glasgow

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Presentations

Fractional Flow Reserve versus Angiography in Guiding Management to Optimise Outcomes in Non-ST Elevation Myocardial Infarction (FAMOUS – NSTEMI). Clinical Trial: Relationships Between FFR and Angiographic Stenosis Severity at Baseline. Layland J., Curzen N, Sood A, Das R, Balachnadrán K, Junejo S, Lee M, Mahrous A, Ahmed N, Shaukaut A, Teng V, O'Donnell A, Petrie M, Eteiba H, Watkins S, Lindsay M, McEntegart M, Davie A, Henderson R, Papworth R, McConochie A, Oldroyd K, Berry C. TCT San Francisco 2013.

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T1 and T2 Mapping have a higher diagnostic accuracy for the ischaemic area-at-risk in NSTEMI patients compared with dark blood imaging. Layland J, McClure J, Carrick D, Rauhalampi S, Watkins S, O'Donnell A, Sood A, Oldroyd K, Berry C. Society of Cardiovascular and Magnetic Resonance Conference. New Orleans 2014.

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Prizes

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Summary

A prospective randomised controlled clinical trial of treatment decisions informed by invasive functional testing of coronary artery disease severity compared with standard angiography-guided management was implemented in 350 patients with a recent non-ST elevation myocardial infarction (NSTEMI) admitted to 6 hospitals in the National Health Service. The main aims of this study were to examine the utility of both invasive fractional flow reserve (FFR) and non-invasive cardiac magnetic resonance imaging (MRI) amongst patients with a recent diagnosis of NSTEMI. In summary, the findings of this thesis are: (1) the use of FFR combined with intravenous adenosine was feasible and safe amongst patients with NSTEMI and has clinical utility; (2) there was discordance between the visual, angiographic estimation of lesion significance and FFR; (3). The use of FFR led to changes in treatment strategy and an increase in prescription of medical therapy in the short term compared with an angiographically guided strategy; (4) in the incidence of major adverse cardiac events (MACE) at 12 months follow up was similar in the two groups. Cardiac MRI was used in a subset of patients enrolled in two hospitals in the West of Scotland. T1 and T2 mapping methods were used to delineate territories of acute myocardial injury. T1 and T2 mapping were superior when compared with conventional T2-weighted dark blood imaging for estimation of the ischaemic area-at-risk (AAR) with less artifact in NSTEMI. There was poor correlation between the angiographic AAR and MRI methods of AAR estimation in patients with NSTEMI. FFR had a high accuracy at predicting inducible perfusion defects demonstrated on stress perfusion MRI.

This thesis describes the largest randomized trial published to date specifically looking at the clinical utility of FFR in the NSTEMI population. We have provided evidence of the diagnostic and clinical utility of FFR in this group of patients and provide evidence to inform

larger studies. This thesis also describes the largest ever MRI cohort, including with myocardial stress perfusion assessments, specifically looking at the NSTEMI population. We have demonstrated the diagnostic accuracy of FFR to predict reversible ischaemia as referenced to a non-invasive gold standard with MRI. This thesis has also shown the futility of using dark blood oedema imaging amongst all comor NSTEMI patients when compared to novel T1 and T2 mapping methods.

Preface

I had a substantial role in all studies submitted in this thesis. Firstly I was actively involved in planning and organising the FAMOUS NSTEMI study from the outset long before the trial began. I worked closely with the Robertson centre in the genesis of the electronic clinical research form (eCRF) and the planning of the statistical analysis for FAMOUS. I visited every site at least twice to perform site initiation visits and data monitoring. I recruited patients at the Golden Jubilee hospital and every patient at Hairmyres hospital. I entered patient details in the eCRF and was involved in patient follow up. For the MRI substudy, I recruited all patients in this substudy that were performed at the Glasgow Cardiovascular Research Centre (GCRC). For those patients imaged prior to their angiogram I recruited them directly from the Western Infirmary, Glasgow. I supervised all of the MRI scans and coordinated patient transport for the appointments. I coordinated and performed all MRI analysis. I performed all statistical analysis in the studies involved however, the analysis for FAMOUS had to be performed independently by the Robertson centre as the trial was randomised in order to protect the integrity of the study.

Chapter 1 – Introduction and Literature Review

1.1.1 Epidemiology and Burden of Disease

Ischemic heart disease (IHD) is a condition characterized by inadequate oxygen delivery to the myocardium that is most commonly a consequence of coronary artery disease (1). It is a major cause of morbidity and mortality contributing approximately 30% to total worldwide deaths(2). It is estimated that 1,065,000 will have an acute coronary syndrome (ACS) annually (3). The deaths attributable to coronary and cardiovascular disease significantly out shadow deaths from cancer. The lifetime risk for developing coronary heart disease (CHD) after the age of 40 is 49% in men and 32% in women(3-5). Significant progress has been made in the management of CHD and ACS. Through these efforts, the mortality from myocardial infarction has significantly reduced and the management of patients with angina has improved (6, 7).

Ischaemic heart disease can manifest as stable angina or unstable clinical syndromes that include unstable angina, non-ST segment elevation myocardial infarction {NSTEMI and ST-segment elevation myocardial infarction {STEMI} with the two disease processes having distinct pathophysiological differences (Refer to Figure 1). NSTEMI shares similar pathophysiology to unstable angina but results in greater myocardial injury.

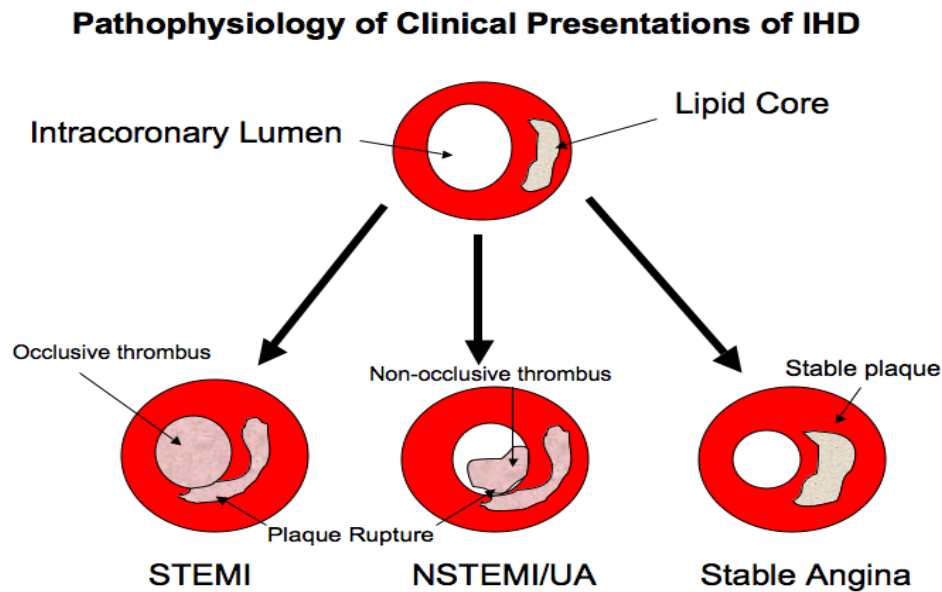


Figure 1: Pathophysiology and Clinical Presentations of Patients with Ischaemic Heart Disease.

Stable angina represents the more prevalent clinical manifestation of ischaemic heart disease with an estimated 20 000–40 000 individuals per million suffering from angina in European countries (1). Available data, from multiple studies suggest an annual incidence of uncomplicated angina pectoris of approximately 0.5% in western populations (8, 9). Estimates for annual mortality rates in patients with stable angina range from 0.9–1.4% per annum (10, 11), with an annual incidence of non-fatal MI between 0.5% and 2.6% (11, 12) in this group.

NSTEMI is the commonest form of acute myocardial infarction and a leading global cause of premature morbidity and mortality (6). Recent studies have demonstrated a significant reduction in the incidence of STEMI over recent years whereas NSTEMI incidence has remained stable (6). Annual mortality rates from Europe have shown a non-significant mortality difference between STEMI and NSTEMI being 9% and 11.6% respectively (13). However, recent data reported by investigators in the United States have

shown a significant mortality difference between the two groups. McManus and colleagues demonstrated a 1-year mortality rate of 8.4 % in the STEMI cohort versus 18.7% in the NSTEMI group (4). The recent Acute Coronary Syndrome Prospective Audit (ACACIA) registry showed 1 year mortality of 8% for STEMI and 10.5% for NSTEMI (14).

1.1.2 Pathophysiology of NSTEMI/UA

The pathogenesis of NSTEMI is thought to be due to a number of processes. Firstly, rupture or erosion of an unstable vulnerable atheromatous plaque with a superimposed non-occlusive thrombus causing reduced myocardial perfusion, ischemia, and ultimately necrosis. Plaque instability is accelerated by inflammation of the arterial wall and by the expression of metalloproteinases present in T lymphocytes in the shoulder of the plaque; these enzymes are thought to attack the thin fibrous wall of the plaque (15).

The major components of coagulation that is, the platelets and the coagulation cascade, play critical roles in thrombus formation. Plaque rupture or erosion exposes platelets to subendothelial collagen initiating platelet adhesion to the damaged endothelium. This adhesion activates platelets leading to morphological changes. Multiple platelet agonists, such as adenosine diphosphate (ADP), thromboxane, and epinephrine, lead to a conformational change of the glycoprotein (GP) IIb/IIIa receptor on the platelets' surface that binds them to fibrinogen, resulting in platelet aggregation and the formation of a "platelet plug." Down-stream microembolization of platelet aggregates and plaque debris often causes distal myocardial necrosis. The exposure of tissue factor activates the coagulation cascade; its combination with factor V leads to the activation of coagulation factor X to form factor Xa, which in turn leads to the conversion of factor II (prothrombin) into factor IIa (thrombin); the latter is responsible for the conversion of fibrinogen to fibrin, which traps platelet aggregates, thereby forming a thrombus (16).

The use of biochemical markers such as high-sensitivity C-reactive protein as well as intravascular imaging in the form of intravascular ultrasound and optical coherence tomography, have all confirmed the evidence of an inflammatory milieu evident in the coronary arteries of ACS patients with obstructive disease (17-20). In patients with obstructive disease without an overt inflammatory state enhanced sympathetic nervous system activation may cause changes in cardiovascular physiology that can result in plaque instability and subsequent ACS (21).

Coronary artery vasoconstriction, which may involve both the epicardial and microcirculation as occurs in adrenergic-mediated constriction, in cocaine abuse, and coronary syndrome X is also implicated in the pathogenesis of ACS. Moreover, NSTEMI can also occur as a result of an imbalance between myocardial oxygen supply and demand, secondary to increased oxygen demand as can occur in conditions such as tachyarrhythmias, fever, anaemia or sepsis with or without underlying coronary artery disease (22). These pathogenetic processes of NSTEMI are not mutually exclusive and one or more may be causal on an individual patient basis.

1.1.3 Diagnosis of NSTEMI(23)

History

The clinical presentation of NSTEMI encompasses a wide variety of symptoms. Traditionally, several clinical presentations have been distinguished:

- Prolonged (20 min) anginal pain at rest;
- New onset (de novo) angina (Class II or III of the Classification of the Canadian Cardiovascular Society¹¹);
- Recent destabilization of previously stable angina with at least Canadian Cardiovascular Society Class III angina characteristics (crescendo angina);

- Post-MI angina.
- However, it can also present in a more atypical fashion with increasing breathlessness and rarely syncope.

ECG

The resting 12-lead ECG is the first-line diagnostic tool in the assessment of patients with suspected NSTEMI and it is recommended that it should be obtained within 10 min after first medical contact. The characteristic ECG abnormalities of NSTEMI are ST-segment depression or transient elevation and/or T wave changes (24). It should be appreciated that a completely normal ECG does not exclude the possibility of NSTEMI. In particular, ischaemia in the territory of the circumflex artery or isolated right ventricular ischaemia may not be associated with abnormalities on the 12-lead ECG (25).

Biomarkers

Measurement of circulating cardiac troponin concentrations play a central role in establishing a diagnosis and stratifying risk and make it possible to distinguish between NSTEMI and unstable angina. In patients with MI, an initial rise in troponins occurs within 4 hours of symptom onset and can remain elevated for up to 2 weeks. In NSTEMI minor troponin elevations usually resolve within 48-72 hours (23). An elevated troponin predicts short-term rates of myocardial infarction and death and also outcomes into the longer term. It is also widely used to guide management decisions and identify patients who may benefit from an early invasive strategy. However, troponin should not be used as a sole decision criterion for invasive management as certain high-risk troponin negative subgroups have an in-hospital mortality of 12.7% (26). The emergence of troponin tests with even higher sensitivity (i.e. detection of troponin concentration in nanograms / litre), is likely to compound the diagnosis and management of ACS patients even further. The incidence of

NSTEMI is likely to rise but the diagnostic concordance with hs-troponin elevations with plaque rupture, and the prognostic implications, are uncertain.

1.1.4 Risk stratification in patients with NSTEMI

Current guidelines advocate that all patients with NSTEMI be risk stratified following diagnosis. This strategy enables the physician to decide on an immediate management strategy and also provide the patient with an idea about their future prognosis. Some patients with NSTEMI do not require risk stratification for obvious reasons e.g. cardiogenic shock and ongoing chest pain. However, most patients with NSTEMI will require risk stratification. The most commonly applied tools in use are the TIMI risk score and the GRACE risk score. The utility of such scores is in identifying patients who would benefit from an early invasive strategy of coronary angiography. For example, a GRACE score of >140 is an established cut-off for a patient being high risk and requiring early invasive therapy(27).

However, despite the use of clinical history, ECG, biomarkers and risk stratification tools, approximately 9-14% of patients with a NSTEMI who undergo angiography have no significant coronary stenosis (28-30). When compared to patients with obstructive culprit disease, patients without significant disease have a much better short-term prognosis. Similar findings were reported in the CRUSADE registry whereby NSTEMI patients without significant coronary disease had a lower in-hospital death rate (30). Therefore despite appropriate use of risk models to identify patients who may benefit from early intervention, clearly there is a need for improved methods of identification to complement current risk tools.

1.1.5 Role of Non-Invasive Testing

Clinical guidelines do not recommend non-invasive stress testing in patients with recent NSTEMI because the reference diagnostic test is invasive coronary angiography,

which is also used to guide PCI. However, in situations of diagnostic uncertainty the use of non-invasive imaging can be helpful. Echocardiography is useful in assessing ventricular function, but regional dysfunction may be present in acute ischaemia as well as old infarction. Myocardial perfusion imaging at rest identifies one or more areas of hypoperfusion in almost all patients with NSTEMI, but as is the case with echocardiography cannot distinguish clearly between acute ischemia and old infarction (31) Computed tomographic coronary angiography is being used with increasing frequency in emergency departments, especially in patients deemed to be at low risk of having ACS (32). Its use in this manner is to exclude a severe coronary stenosis results in a high negative predictive value with the potential for earlier discharge from hospital but an increase in the rate of invasive coronary angiography (33). Cardiac MRI can simultaneously assess global and regional left ventricular function, perfusion, and myocardial viability (34) and will be discussed in greater detail later in this thesis.

Summary

Thus despite clear diagnostic criteria and well validated methods for risk stratifying patients there remains a need for further methods to improve patient selection for an invasive approach in NSTEMI.

1.2 MRI in NSTEMI

As has already been alluded to thus far, there are many issues regarding the diagnosis and risk stratification of patients with NSTEMI. Risk stratification tools such as GRACE and the TIMI risk score allow for selection of higher risk patients to undergo an invasive strategy. However, even using these scores, many patients undergoing coronary angiography for NSTEMI have normal coronary arteries. Therefore, new techniques that allow for improved

risk stratification and thus improved patient selection are needed. Novel cardiac MRI techniques may provide such a tool.

1.2.2 The Ischaemic Area-at-Risk

The jeopardised region of acutely hypoperfused myocardium within a coronary distribution during coronary occlusion is defined as the area-at-risk (AAR) of infarction (35). Without prompt restoration of blood flow, myocardial necrosis within the perfusion territory will ensue as a 'wavefront' from the subendocardium to the subepicardium. Importantly, the wave of irreversible injury is preceded by reversible injury of the entire AAR (36). Treatment strategies such as revascularisation techniques and pharmacological therapies aim to salvage areas of acutely ischemic, but reversibly injured, myocardium. Thus non-invasive imaging methods that can delineate the jeopardised AAR and potentially salvageable myocardium are important in assessing the efficacy of such therapies and may potentially guide appropriate patient selection in some patients with ACS. For patients with myocardium at risk, early intervention is beneficial (37) however, for patients without myocardium at risk an invasive strategy confers no benefit.

Thus a diagnostic approach that identifies myocardium at risk within the heterogeneous NSTEMI population could facilitate timely coronary angiography and revascularisation and concentrate resource use.

Cardiac MRI (CMR) is a noninvasive technique for assessing heart structure and function without the need for ionizing radiation and is an increasingly utilized technique in the assessment of patients with ischaemic heart disease. The physics and technology of CMR enables the creation of a powerful magnetic field, often at either 1.5 or 3.0 Tesla that when applied, allows protons (hydrogen atoms) within the body to align either parallel or anti-parallel to this field. This creates a net magnetic vector, allowing a radiofrequency (RF) pulse

to then be applied, which delivers energy to the protons and causing them to align in a different direction (transverse or perpendicular). On cessation of the RF pulse, the hydrogen atoms return back to their original (equilibrium) state, releasing energy and emitting a signal as they do so. This signal is then picked up and turned into an image (34). CMR technology has overcome many of the challenges with cardio-respiratory motion to provide clinically useful imaging scans.

The potential for CMR in the diagnosis and management of patients' with NSTEMI is based upon the principle that acute myocardial injury is associated with multiple metabolic and structural changes leading to oedema in the affected perfusion bed, before the onset of irreversible injury. This higher water content in ischaemic territories is associated with higher T2 relaxation times (38) a contrast generating effect that can be used by CMR. Extensive preclinical and human studies have established that T2 signal hyperintensity by cardiac magnetic resonance (CMR) indicates increased myocardial water content (35) T2 may increase within 30 min of ischaemia and remains elevated for 2 or more weeks following the initial ischaemic insult rendering it useful in the retrospective assessment of the AAR and for defining the culprit myocardial territory that is often challenging in NSTEMI patients due to the high incidence of multivessel disease (39).

Cardiac MRI characterises different tissues based on their specific nuclear magnetic properties, including T1 and T2. Simplistically, T1 relaxation time is the rate constant that describes how quickly protons realign with the main magnetic field back to their equilibrium state. T2 relaxation time is the rate constant that describes how long protons remain synchronous or "in phase" after being tipped perpendicular to the main magnetic field by a RF pulse (34).

As the heart is a moving organ images are acquired over several heartbeats, with breath-holding and ECG gating employed to allow synchronisation to the correct phase of the

cardiac cycle.

1.2.2 Cardiac MRI: a “one-stop-shop” for a comprehensive assessment early after MI

Cardiac MRI has several applications in the acute phase of MI, including assessing myocardial function through cine imaging, detecting myocardial oedema (denoting the ischaemic AAR) and therefore allowing myocardial salvage to be calculated) through T2-weighted (T2W) imaging and identifying irreversible myocardial injury through late gadolinium enhancement (LGE) imaging(34).

Moreover, several studies have shown that single-photon emission computed tomography (SPECT) and photon emission tomography (PET) may miss cases of sub-endocardial necrosis due to the limited spatial resolution of these methods whereas these abnormalities may be detected by MRI which has higher spatial resolution (40-42). Therefore, cardiac MRI has higher diagnostic accuracy for myocardial necrosis and tissue viability than all other non-invasive imaging methods.

1.2.3 T2 and T1 weighted imaging to assess myocardial oedema and area at risk (AAR)

T2-weighted (T2W) imaging identifies increased myocardial water content through increased signal intensity (35). Myocardial oedema is a natural consequence of acute myocardial infarction (AMI) and includes both irreversibly damaged and potentially salvageable myocardium, in the case of prompt reperfusion (43). Using the principles of T2W imaging, to detect myocardial oedema, AAR can be quantified. This method for identifying the AAR has been validated against AAR determined by histopathology as well as AAR obtained by angiographic measurements (44-46)

Even transient ischaemia can produce differences in the myocardial longitudinal (T1) and transverse (T2) relaxation times, and newer techniques have shown improved sensitivity

in identifying the culprit territory amongst patients with AMI (47, 48). Dark-blood fat-suppressed (short tau inversion recovery, STIR) T2-weighted MRI methods (T2W STIR) are widely used for clinical and research purposes (37, 49). Following its development by Simonetti and colleagues dark blood STIR oedema imaging has enjoyed widespread use to assess for the presence of myocardial oedema (49). Indeed several investigators have shown prognostic information using STIR imaging. For example, in a prospective study involving 88 patients with NSTEMI, Raman and colleagues highlighted the potential for T2-STIR imaging in identifying oedematous myocardium and to distinguish patients requiring coronary revascularization from those that did not.

Moreover, the presence of oedema was associated with a higher hazard of a cardiovascular event or death within 6 months after NSTEMI (37). Yet, despite great theoretical promise, the clinical reality of using dark blood T2-STIR imaging has been far from optimal due to methodological problems inherent with the technique. These include sensitivity of the sequence to artifacts from respiratory and cardiac motion, the variability in myocardial signal related to surface coil intensity inhomogeneity, and the subjectivity of image interpretation (50, 51). Thus, a more reliable method of assessing the T2 signal alteration may increase the clinical utility of T2 oedema imaging potentially leading to wider adoption.

Bright-blood T2-weighted MRI techniques have recently emerged as potential alternatives to dark-blood T2-weighted MRI. Kellman and colleagues developed a bright-blood T2-prepared, single-shot steady-state free precession (T2-prepared SSFP) method, which involves surface coil intensity normalization; parallel imaging techniques, and motion-corrected averaging (52). The group demonstrated improved diagnostic confidence in detecting acute from chronic AMI compared with dark blood imaging. Moreover, Aletras and colleagues developed another bright-blood T2-weighted method, ACUT2E (Acquisition for

Cardiac Unified T2 Oedema), which is a hybrid of turbo spin-echo (TSE) and SSFP(53). The TSE-SSFP method has higher signal-to-noise (SNR) and contrast-to-noise (CNR) ratio than T2-prepared SSFP. A non contrast, quantitative T2 mapping sequence using T2-SSFP has also been proposed and been shown to be more accurate than conventional T2 STIR at predicting AAR in animal and human models (45, 54).

Just as with T2, recent experimental studies have shown that T1 values increase with increasing myocardial water content and thus with ischaemia and infarction (45) By directly quantifying T1 values for each voxel in the myocardium, a parametric map can be generated representing the T1 relaxation times of any region of the heart. The most widely used T1-mapping sequence is based on the Modified Look- Locker Inversion-recovery (MOLLI) technique that consists of a single shot TrueFISP image with acquisitions over different inversion time readouts allowing for magnetization recovery of a few seconds after 3 to 5 readouts(55).In addition to MOLLI, a shortened breath-hold adaptation with conditional curve fitting (ShMOLLI) (56) was proposed as a means of mitigating some of the potential issues with MOLLI such as the heart rate dependence. However, MOLLI remains the most widely used of the T1 mapping techniques.

1.2.4 Dark Blood versus Newer T1/T2 Techniques for Area at Risk Assessment

Our group has recently demonstrated the superior accuracy of bright blood T2 weighted imaging to detect the ischemic AAR when compared to conventional dark blood STIR imaging. In this cohort of 54 consecutive AMI patients Bright-blood T2 weighted imaging had greater accuracy for the identification of the infarct related artery as well as more accurate assessment of the ischaemic area at risk. However, this was a study performed at 1.5Tesla with the majority of patients presenting with STEMI (44 patients 81%) (57).

In a canine model of ischaemia and using a microsphere reference standard, Ugander and

colleagues compared T1 (ShMOLLI) and T2 maps at 1.5 T for defining the area at risk. Both imaging modalities demonstrated equivalence with excellent correlation(45)Ferreira and colleagues investigated the diagnostic performance of dark blood imaging when compared to Bright Blood (ACUT2E) imaging as well as a novel T1 mapping method (ShMOLLI) in patients with Takotsubo cardiomyopathy and oedema syndromes without infarction at 1.5 Tesla (58). The group demonstrated superior diagnostic accuracy with T1 mapping when compared to both dark blood and bright blood T2 imaging methods. Verhaert and colleagues have also demonstrated superior accuracy of a novel T2 mapping technique when compared with dark blood imaging at 1.5 Tesla (54). Amongst 27 patients - only 11 of whom presented with NSTEMI, the use of T2 maps was associated with more reliable and improved detection of oedema.

Recently, Dall'Armellina and colleagues assessed the use of T1 with T2 mapping amongst 41 patients presenting with myocardial infarction at 3.0 Tesla (48). 73% of the study cohort presented with STEMI. There was a similar diagnostic performance of T1 vs. T2 maps for detecting edematous injured myocardium. In a subgroup analysis performed in only 9 patients with NSTEMI, the authors demonstrated a superior diagnostic performance of T1 maps over T2 maps and also less variability in T1 compared with T2 maps.

Thus although the shortcomings of dark blood imaging are well described, there is a lack of published data in a large NSTEMI cohort particularly at 3.0 Tesla. There is also a lack of data comparing T1 versus T2 maps in the NSTEMI population. Previous studies comparing dark blood imaging with newer T2 or T1 methods have included only small numbers of patients with NSTEMI.

1.2.5 The Angiographic Area at Risk

Using CMR and tracing the endocardial surface area of an infarct, several

angiographic scores have been developed and validated amongst patients with ACS to reflect the AAR (59). Moreover, the APPROACH score has been shown to correlate with T2 weighted myocardium at risk using bright blood imaging (44). In general, there is increasing strength of relationship between the angiographic area at risk and a greater degree of infarct transmural extent (59). Typically, NSTEMI patients have smaller, less transmural, sub-endocardial infarcts and thus it is unclear whether angiographic scores describing the AAR will correlate with CMR AAR in NSTEMI. In the populations studied and reported on thus far, the mean infarct size in these subpopulations have been moderate; 16.7% reported by Payne et al (57) with a mean troponin of 50mg/dl reported by Verhaert and colleagues(54). Whether the relationship between angiographic area at risk will hold true for smaller infarcts seen in NSTEMI is unknown.

1.2.6 Potential Utility of CMR in NSTEMI

Since edema persists for days or weeks after an acute ischaemic injury, STEMI patients have generally been studied following revascularisation, a time when potential benefit of identifying the AAR is limited. NSTEMI is a condition typified by smaller degrees of myocardial injury and non-occlusive culprit lesions. Compared with STEMI, the clinical utility of identifying the AAR in NSTEMI patients could theoretically have a greater diagnostic and clinical role since NSTEMI is a more heterogeneous condition and MRI can be performed prior to revascularisation. However, data allowing direct comparison of T1/T2 mapping sequences and T2W STIR in NSTEMI, particularly at 3.0 Tesla, are lacking.

Furthermore, the use of edema imaging suggests a further role for cardiac MRI in the diagnosis and early assessment of patients presenting with chest pain syndromes(37). This may enable patients who have unstable angina but with no changes in troponin levels to be identified and further direct the interventional cardiologist towards the likely culprit vessel

(39).

Myocardial Haemorrhage

T2W imaging detects regions of myocardial haemorrhage, as identified by a hypointense core within regions of high-signal myocardial oedema. Myocardial haemorrhage occurs during the successful post-reperfusion phase of MI, representing severe microvascular injury, specifically damage to the endothelial barrier, which allows blood to leak into the surrounding myocardial tissue(60).

The presence of myocardial haemorrhage in patients with AMI has been shown to have a greater AAR, lower pre-PCI thrombolysis in myocardial infarction (TIMI) flow and a larger final IS (61). Furthermore, myocardial haemorrhage has also been shown to be the strongest predictor of LV remodelling at 3 months, independent of the IS (62).

In recent years, new cardiac MRI techniques have become increasingly recognised to detect myocardial haemorrhage, namely T2* weighted sequencing and T2* mapping(63, 64). These have been historically used to detect iron overload in patients with haematological disorders dependent on regular blood transfusions, such as those with thalassaemia or myelodysplasia (64). These techniques are more specific than T2W imaging for the detection of myocardial haemorrhage. This gives a unique perspective on infarct pathology, with myocardial haemorrhage potentially having a role as an outcome measure and may represent a novel therapeutic target. However, published work has been almost exclusively been in the STEMI cohort with very little in NSTEMI. Thus, not only is the impact of myocardial haemorrhage on prognosis unknown amongst patients with NSTEMI, the incidence of haemorrhage in this population is not well studied.

1.2.7 Late Gadolinium enhancement (LGE): assessment of scar and viability

LGE images are T1 weighted sequences that involve the acquisition of a series of short-axis slices of the ventricles as well as 2-chamber, 3-chamber and 4-chamber axis views. These images are obtained approximately ten to fifteen minutes after an intravenous administration of a gadolinium (extracellular) based contrast agent (65).

In the acute phase of MI, gadolinium enters the intracellular space through damaged cell membranes where it is retained (66). Conversely, in normal myocardium, the presence of densely packed healthy myocytes means that gadolinium is “washed out,” more rapidly. The effect is an increase in gadolinium concentration, in infarcted myocardium, shortening T1 relaxation time and thus resulting in hyper-enhancement compared to non-enhanced viable regions (67). In other words, it assumes a bright signal as opposed to the dark viable myocardium, identifying areas of irreversible myocardial injury (67). This is currently the gold standard for *in vivo* infarct visualisation. Essentially, LGE differentiates irreversibly damaged (non-viable) myocardium, from myocardium which is simply stunned following an acute ischaemic insult, with acute reversible myocardial injury being oedema positive but LGE negative.

Furthermore, LGE imaging can evaluate the extent of transmural necrosis. The transmural extent of MI is an important predictor of functional recovery, with an inverse relationship seen between the transmural extent of MI and the recovery of contractile function (68, 69). This information provides the cardiologist with insights as to the potential benefit from revascularisation, in patients with AMI(69). As a general rule of thumb, if the transmural extent of LGE is greater than 50%, then there is less likely to be functional recovery following revascularisation(34).

1.2.8 Microvascular Obstruction (MVO)

LGE imaging also has the ability to identify another microvascular injury characteristic known as microvascular obstruction (MVO) (68, 69). The presence of MVO represents more severe ischemic injury and is directly correlated with larger infarct size(70). This can be seen on MRI as a central hypo-intense core, as shown by the dark zones, within bright regions of LGE (71)

Moreover, a strong relationship exists between MVO and myocardial haemorrhage, with the size of the “dark zones,” on LGE images correlating with the extent of myocardial haemorrhage (72). Interestingly, MVO is present in all patients with myocardial haemorrhage but not every patient with MVO will have myocardial haemorrhage. MVO has not been well studied in NSTEMI compared with STEMI. The recently published Effect of Aspiration Thrombectomy on Microvascular Obstruction in NSTEMI (TATORT-NSTEMI) trial examined the impact of routine aspiration thrombectomy for patients with NSTEMI (73). The study failed to show a benefit of aspiration thrombectomy but did show a prevalence of MVO of approximately 31%. However, this was a highly selected population of high risk NSTEMI patients who had thrombus containing culprit lesions. Thus the reporting of MVO may be higher in this population compared with a more broad NSTEMI population undergoing invasive evaluation and CMR. Indeed Guerra and colleagues reported an incidence of MVO of 13.8% amongst 190 patients with NSTEMI undergoing CMR (74).

1.2.9 Perfusion imaging

Perfusion imaging is used in the assessment of myocardial blood flow, including patency of the microvasculature hence identifying MVO (75). This technique recognises regional blood flow within the myocardium, through changes in T1 weighted signal intensity, after the bolus of contrast administered passes through the myocardium.

Stress perfusion imaging, performed after administration of a vasodilator medication, such as adenosine, can accurately identify flow-limiting lesions within the coronary arteries (76). Plein and colleagues examined the use of stress perfusion MRI amongst patients with NSTEMI of which only 53% had a positive troponin (75). The group compared stress perfusion CMR defects with an angiographic stenosis of at least 70% on coronary angiography. The group found a sensitivity of 88%, specificity of 83%, negative predictive value of 59% and a positive predictive value of 96%. Whilst encouraging, the results of perfusion CMR in this population were not optimal. One major methodological concern with the study however, is the use of stenosis severity at coronary angiography as a gold standard. The patients were also lower risk with only 50% having a positive troponin. Thus the use of stress perfusion CMR may be more accurate at predicting haemodynamically significant stenosis if a more robust marker e.g. FFR was utilised.

Potential Limitations of cardiac MRI

For all that cardiac MRI has to offer, it is constrained by a few important limitations. Cardiac MRI is a high specification technology that involves strong magnetic fields (typically 1.5 – 3.0 Tesla), a protocol of radiofrequency pulse sequences and administration of an intravenous contrast agent. MRI is not possible in patients who are claustrophobic or who have metallic implants. Unlike echocardiography, MRI cannot be performed at the bedside and requires a skilled multidisciplinary team for each scan. MRI may not be possible in the sickest patients including those with pulmonary oedema (who may be unable to lie flat), patients with arrhythmias or those who may not be able to breath-hold to minimise cardiorespiratory motion. New pulse sequences, such as T2-mapping (for the detection of myocardial oedema and AAR), use motion-correction and arrhythmia rejection algorithms to help overcome these limitations.

As discussed, cardiac MRI may involve the use of a gadolinium based contrast agent, which has been related to nephrogenic systemic fibrosis (NSF), especially in patients with severe renal impairment. NSF is a systemic fibrosing disorder of the skin, connective tissue, joints, liver muscles and heart, progressing rapidly within a short space of time. Therefore, it is of importance to evaluate renal function prior to MRI, particularly if there are signs of renal complications post-angiography. However, this complication is rare and no reports of NSF have occurred in patients with a glomerular filtration rate of $>30\text{ml/min}$.

Finally, cardiac MRI is expensive compared to other imaging methods such as echocardiography and even nuclear imaging. More research is needed to determine whether or cardiac MRI may be cost effective when used in this way in routine clinical practice.

Summary

The use of CMR in patients with NSTEMI holds a promising future and is fast becoming a widely used tool in the assessment of STEMI, providing more than just standard anatomical, functional and haemodynamic information. There remains a lack of data in the utility of novel edema imaging methods amongst patients with NSTEMI and their diagnostic utility compared with established dark blood techniques. Furthermore, there is a lack of robust data on the use of stress perfusion CMR in this population.

1.3 Role of Coronary Angiography

Coronary angiography has vastly improved our understanding of coronary artery disease providing an unrivalled appreciation of coronary anatomy and plaque distribution. It has a temporal resolution of 7.5 – 20 frames/second and a spatial resolution of $\sim 150 - 300\ \mu\text{m}$. Invasive coronary angiography is the reference diagnostic tests for determining the presence and extent of coronary artery disease. However, due to the inherent complications

involved with invasive coronary angiography it is not recommended for every patient with ischaemic heart disease. In general, coronary angiography is recommended for patients with symptomatic stable angina with high pretest probability for coronary artery disease (1). It is also recommended for all intermediate to high risk NSTEMI patients in order to qualify coronary artery anatomy and identify patients who would benefit from revascularisation (77). For patients presenting with STEMI coronary angiography is also indicated in the setting of emergency primary PCI (78). It is also indicated following an initial non-invasive reperfusion strategy (78).

Although regarded as the gold standard in the evaluation of coronary artery anatomy, coronary angiography possesses limitations. Autopsy and intravascular ultrasound studies have demonstrated the shortcomings of coronary angiography in determining the extent of atherosclerotic disease (79). Coronary arteries are three-dimensional structures and fluoroscopic coronary angiography provides a planar silhouette of the contrast filled lumen. The coronary angiographic severity of lesions is also described in relation to a distal 'normal' reference segment. Necropsy studies have demonstrated that in patients with atherosclerosis, disease is frequently diffuse without normal segments (80). This has obvious implications in interpreting angiographic images. Lesion eccentricity, foreshortening and vessel overlap are also factors contributing to the subjective angiographic evaluation of coronary arteries (79). Furthermore, coronary angiography only provides information on the epicardial circulation, providing little data on other major constituents of myocardial blood flow that has recently been shown to be of significant importance at determining prognosis over and above epicardial flow(81).

Intravascular ultrasound has also allowed *in-vivo* appreciation of this extent of plaque burden as well as the nature of arterial remodelling, a process defined by changes in the vascular dimensions that occur early in the development of atherosclerosis. Positive

remodelling refers to an increase in the diameter of the external elastic membrane to compensate for underlying atheroma in order to preserve luminal size [13]. This may also conceal the extent of disease displayed with coronary angiography [11].

The assessment of intermediate lesions defined as a luminal narrowing with a diameter stenosis $\geq 40\%$ but $\leq 70\%$ [10] are particularly challenging and incorrect management decisions can be made if based solely on angiographic severity in this intermediate group. Specifically, in patients with NSTEMI, rather than vessel occlusion as is usually the case with STEMI, patients may present with non-occlusive, intermediate severity stenosis. Thus decision-making that relies solely on coronary angiography may be problematic.

1.3.1 Pitfalls in visual assessment

Invasive management strategies are generally delivered around visual interpretation of coronary stenoses and revascularization decisions mediated at the discretion of the angiographer. This visual approach has been challenged in light of the evolving and burgeoning role of fractional flow reserve (FFR) in stable coronary artery disease. Clinical judgments as to the haemodynamic severity of coronary stenoses performed visually are subjective and inaccurate leading to misdiagnosis and altered treatment decisions, which can be of prognostic significance (82, 83). In ACS, this challenge is exacerbated in multi-vessel disease found at angiography in trying to identify the culprit vessel since discriminating flow-limiting disease from non-culprit disease can be difficult (84). Up to 60% of patients with NSTEMI can have multi vessel disease and therefore treatment decisions based solely on the angiogram can lead to sub-optimal health outcomes (85).

1.3.2 Multi-vessel Disease

Multi-vessel coronary disease (MVD) is observed in approximately 30-50% of patients presenting with acute ST elevation myocardial infarction (STEMI) and is associated with a worse prognosis(86). In the recently published PRAMI trial, 54% of STEMI cases had MVD as defined by a stenosis of 50% or more in one or more coronary arteries other than the infarct related artery(87). Likewise, in patients with non-ST elevation myocardial infarction (NSTEMI), 30–59% of patients have MVD(88). In patients with STEMI and MVD, the culprit artery is generally obvious but the functional significance of non-culprit lesions may be difficult to determine. The ability to accurately assess the functional significance of non-culprit stenoses at the time of primary PCI for STEMI would potentially facilitate a strategy of complete revascularisation during the index procedure with consequent health and economic benefits. In patients with NSTEMI and MVD, the same scenario applies but often with the additional difficulty of correctly identifying the culprit itself, an issue that may also be addressed by functional testing in the cath lab.

1.3.2.1 Revascularisation Strategies in Patients with ACS and Multi-vessel Disease

Contemporary guidelines recommend in patients stabilized after an episode of ACS, the choice of revascularization modality can be made as in stable CAD(89). The European Society of Cardiology (ESC) guidelines suggest basing the revascularization strategy in UA/NSTEMI (either culprit only PCI or multi-vessel PCI or CABG) on clinical status and disease severity according to local heart team policy (Class 1/Level of Evidence C)(23). In approximately one-third of patients' angiography will reveal single- vessel disease, allowing ad hoc PCI in most cases. Multivessel disease will be present in another 50%. Here the decision is more complex and the choice has to be made between culprit lesion PCI, multivessel PCI, or CABG. Culprit lesion PCI usually is the first choice in most patients with

multivessel disease. The strategy of multivessel stenting for suitable significant stenoses rather than stenting the culprit lesion only has not been evaluated appropriately in a randomized fashion. Culprit lesion PCI does not necessarily require a review by the heart team when on clinical or angiographic grounds the procedure needs to be performed ad hoc after angiography(23).

In patients with STEMI, it is recommended that primary PCI should be limited to the culprit vessel with the exception of cardiogenic shock and persistent ischaemia after PCI of the supposed culprit (Class 2a/Level of Evidence B). If staged PCI to non-culprit vessels is being considered non-invasive stress testing (myocardial perfusion scintigraphy, stress echocardiography, PET or MRI) should be used for ischaemia and viability testing prior to a decision to proceed with PCI(90)

These latter recommendations were based on observational data suggesting that PCI of a non-culprit artery at the time of PPCI in patients with STEMI was associated with increased mortality at 90 days(91, 92). Specifically in a cohort analysis from the HORIZONS-AMI trial, multi-vessel PCI at the time of PPCI was associated with a higher 1-year mortality (9.2% vs. 2.3%) and stent thrombosis rate (5.7% vs. 2.3%) than staged PCI(92). Controversy in this area due to conflicting evidence has led to numerous clinical trials, which are in progress at present, as well as the recently published PRAMI trial. This study demonstrated that in a group of 234 STEMI patients randomised to preventive PCI in non-culprit arteries versus 231 randomised to culprit only PCI there was an absolute 14% risk reduction in the primary outcome (a composite of death from cardiac causes, non-fatal MI, or refractory angina) in favour of preventive-PCI (HR=0.35; 95% CI, 0.21 to 0.58; $P<0.001$)(87). PRAMI used conventional angiographic indices of lesion severity (diameter stenosis > 50%) to identify non-culprit targets for PCI. It is highly likely that some of these lesions were not functionally significant. As such, FFR guidance has the potential to further

target the group of patients/lesions who may benefit from immediate multi-vessel PCI. If however, some or indeed all of the benefit in PRAMI was related to “sealing” of non-culprit but vulnerable plaques then it may be that FFR guided PCI will not be superior to angiographic guidance in this setting (see below). In a similar fashion, there is a lack of data available to guide management of patients with multivessel disease and NSTEMI. Whilst ad-hoc PCI for culprit lesions is suggested, there are no clear guidelines for the management of non-culprit disease.

1.3.3 Identification of the culprit and non-culprit vessels in patients with ACS

Whilst this is frequently straight forward in cases of acute STEMI it can often be difficult to identify the infarct related artery in cases of UA/NSTEMI especially when no localising ECG changes have been observed and no regional wall motion abnormalities are notable on echo. Angiographic features suggestive of acuity include haziness, irregularity, and eccentricity, ulceration, filling defects, thrombus, flow disturbances and sub-total occlusion. Invasive imaging such as optical coherence tomography (OCT) and intravascular ultrasound (IVUS) may enable identification of a ruptured plaque or dissection in difficult cases. FFR has the ability to identify the vessel with physiologically restricted coronary flow and may be useful in identifying the culprit lesion/artery in difficult cases with angiographically diffuse and/or intermediate severity disease. However such a strategy has not been studied prospectively in a randomized control trial.

1.3.3.1 Anatomical and functional lesion assessment in patients with ACS

There are well-founded concerns that the angiographic severity of non-culprit lesions may be overestimated in STEMI due to diffuse vasoconstriction poorly responsive to conventional vasodilators. A study evaluating lesion severity in non culprit vessels in 48 patients imaged within 9 months post STEMI demonstrated that lesion severity decreases

with time, (presumably as thrombus is resorbed and vascular tone normalizes) with minimal lumen diameter on QCA improving from 1.53 +/- 0.51 mm to 1.78 +/- 0.65 mm, ($p < 0.001$) and diameter stenosis from 49.3 +/- 14.5% to 40.4 +/-16.6%, ($p < 0.0001$) (93). This is of concern for patients with NSTEMI where identifying the culprit lesion can be difficult and thus interpreting the angiogram may be even more challenging.

1.3.4 Predicting future events in ACS: Plaque vs. Flow?

It has been demonstrated that up to 80% of patients who present with ACS will have had a stenosis on prior coronary angiography of $\leq 70\%$ that would traditionally be regarded as non-obstructive plaque (94). Further evidence for this originates from two recent landmark studies. The multi-centre prospective natural-history study of coronary atherosclerosis (PROSPECT) study followed 697 patients post ACS who received three vessel virtual histology intravascular ultrasound (IVUS) at baseline and repeat IVUS after presentation with a recurrent ACS. In the follow up period there was a 3 year MACE of 20.9% of which 11.6% were related to the non-culprit artery. Mean stenosis in the non-culprit vessel was only $32 \pm 20.6\%$ at baseline and therefore likely to be visually interpreted as mild. Plaques responsible for MACE were likely to have elevated plaque burden of $> 70\%$, minimal luminal area $< 4.0 \text{ mm}^2$ or to contain thin capped fibroatheromas (TCFA)(95).

The Acute Catheterisation and Urgent Intervention Triage strategy (ACUITY) trial included 7789 patients with ACS who underwent percutaneous intervention following coronary angiography (96). A sub analysis of this trial examined the role of complete versus incomplete revascularization in determining MACE. MACE rates were higher amongst patients who did not achieve complete revascularization. Of interest, a diameter stenosis of $\geq 50\%$ was an independent predictor of MACE at 1 year in the incomplete revascularization group but events also occurred in stenosis $< 50\%$ (97).

Clearly these trials emphasise two potential determinants of future events in patients presenting with ACS. Firstly the characteristics of the plaque itself; TCFA is generally accepted to be the main precursor lesion associated with so called vulnerable plaques and PROSPECT demonstrated that these high-risk plaques were associated with morbidity. Secondly, the extent of residual coronary disease; whether this relates to plaque characteristics or the extent of residual ischaemia is unknown and was beyond the scope of the ACUTY trial. However, they highlight two important areas of future research in patients with ACS i.e. whether residual ischaemia, plaque characteristics or a combination of the two are the main determinants in future morbidity in patients with ACS.

Currently, no prospective study has utilized an invasive anatomical test for vulnerable plaque assessment with concomitant intracoronary haemodynamic testing in either stable or unstable coronary syndromes. The upcoming Fractional Flow Reserve or Optical Coherence Tomography guidance to revascularize intermediate coronary stenosis using angioplasty (FORZA) trial (98) will attempt to assist in answering this question.

1.4 Role of Percutaneous Coronary Intervention

Following Gruentzig's first angioplasty in 1977 the growth of percutaneous intervention (PCI) with the use of stents has been exponential. In Europe the number of stents implanted increased from 3000 in 1992 to 777,000 in 2004 (99). However, this exponential increase has not been met with a corresponding reduction in mortality across all presentations of ischaemic heart disease. Clearly PCI has beneficial effects in specific patient populations but it is not a universal panacea without consequence. Recent evidence has demonstrated that apart from select high-risk subgroups, rather than improve survival, PCI only improves symptoms in patients with stable angina (100). Such equivocal results may be ascribed to the inherent subjectivity that coronary angiography provides in determining the

haemodynamic importance of a coronary stenosis(79). Supportive evidence for this is evident from the nuclear sub-study of the COURAGE trial. In this study patients with a greater reduction in ischemia at clinical follow up had an improved unadjusted survival(101). PCI was superior to optimal medical therapy at reducing the ischaemic burden suggesting that had only ischaemia producing lesions received PCI, the optimal medical therapy with or without PCI for stable coronary disease (COURAGE) trial may have had a different conclusion.

In the NSTEMI cohort, the influence of PCI in determining outcome remains controversial. However, the majority of evidence supports the use of PCI at improving short-term outcomes particularly the need for repeat revascularisation (77). There is also evidence for a survival advantage offered by PCI in certain high-risk NSTEMI subgroups (102). In the STEMI cohort, the evidence for PCI over thrombolysis is well established with PCI offering a more effective strategy for improving both short and long term outcomes(103).

Being an invasive procedure, there is an inherent risk involved with PCI that has been quoted as between 1% and 2% (1). Notwithstanding this risk, there are further complications that can occur as a direct result of coronary intervention that effect the distal coronary microcirculation. These include distal embolisation, microvascular spasm, microvascular thrombosis, inflammation and ischaemia-reperfusion injury (104). Such complications can lead to myocardial ischaemia and infarction. Some investigators have observed that myocardial infarction as a consequence of PCI is associated with reduced survival (105).

1.5 Fractional Flow Reserve

Fractional flow reserve is a validated, simple method of assessing the haemodynamic importance of an epicardial stenosis that can be performed at the time of coronary angiography guiding appropriate revascularisation decisions. Indeed, amongst lesions that are less than 90% in severity, current guidelines mandate the demonstration of ischaemia prior to

revascularization. Both the recent AHA and ESC guidelines have therefore given FFR Level A evidence for guiding revascularization strategy in intermediate lesions(23).

Given the risks of PCI, unnecessary PCI procedures should be avoided wherever possible and objective decision making during coronary angiography is highly desirable. Gould made an important contribution to our understanding of coronary physiology by reporting that resting myocardial blood flow remains normal until an epicardial stenosis reaches $\geq 85\%$ and that hyperaemic blood flow reduces with a $>50\%$ stenosis (figure 2) (106). Using a flow transducer in a dog model, he attempted to define the effect of a stenosis on maximal myocardial flow, rather than resting flow. He defined the coronary flow reserve (CFR) as the ratio of hyperaemic to resting coronary flow and demonstrated that CFR decreased as stenosis severity increased. CFR was later validated against non invasive testing and a value of <2.0 was shown to correlate with the haemodynamic severity of a stenosis (107). However, CFR encompasses both the epicardial and microvascular compartments and is significantly influenced by prevailing haemodynamics and patient specific factors making its routine use unreliable for individual patients at a point in time in the cath lab (108). This conundrum led researchers to investigate other methods for stenosis assessment and it wasn't long before pioneering work from Pijls and De Bruyne developed the concept of an epicardial specific index known as Fractional Flow Reserve (FFR). FFR is defined as the ratio of hyperaemic myocardial flow in the stenotic territory to normal hyperaemic myocardial flow if, theoretically there was no stenosis present (109). More simply it represents the extent to which maximal myocardial blood flow is limited by a stenosis (110).

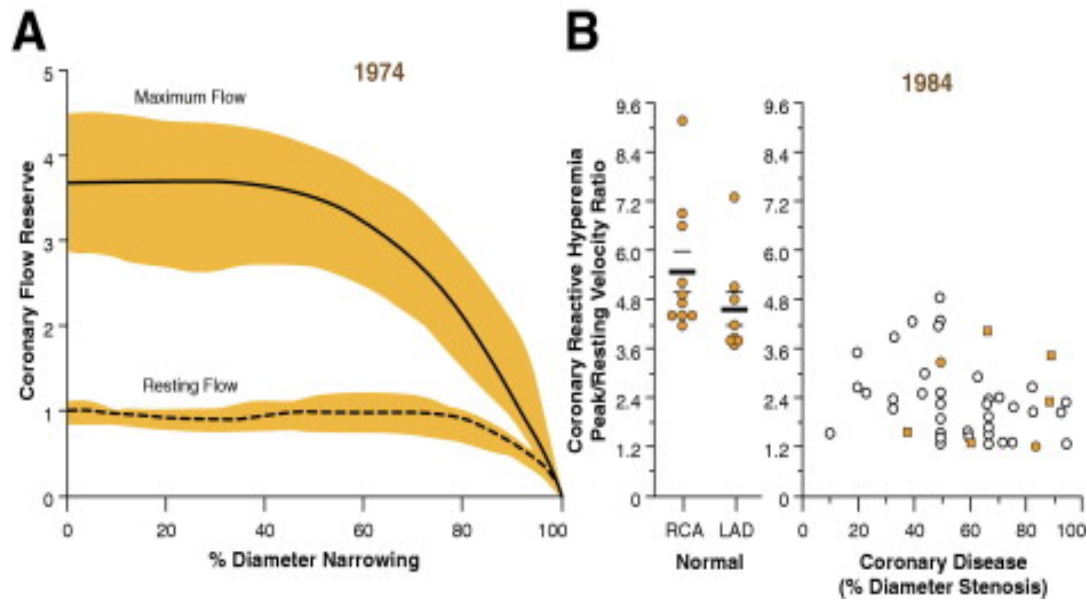


Figure 2: Coronary flow reserve versus arteriographic percent diameter stenosis in canine experimental model. (B) Coronary flow reserve in open-chest humans at bypass surgery versus arteriographic percent diameter stenosis. Solid or open circles or squares indicate different coronary arteries. Reproduced, with permission, from White et al. (12). RCA □ right coronary artery.

1.5.1 Fractional Flow Reserve Theory (Fig. 3)

As with many calculations in cardiovascular physiology, central to the calculation of fractional flow reserve is Ohm's law which states:

$$I = \Delta V / R$$

(where I = current, V = potential difference R = resistance).

This can be extrapolated to the coronary circulation so that:

$$\text{Coronary flow (I)} = \Delta \text{ Pressure} / \text{Resistance (111)},$$

whereby change in pressure is derived from aortic pressure (P_a) minus coronary venous pressure (P_v). In the normal coronary circulation the aortic pressure (P_a) is transmitted to the distal coronary artery without pressure loss and so coronary artery pressure (P_d) is equal to aortic pressure (112). Based upon the Ohm's law coronary derivation, if resistance is kept to

a minimum (with the attainment of maximal hyperaemia), and we assume that venous pressure is constant, we can measure coronary pressure to derive coronary flow. Put another way, during maximal hyperaemia, the coronary pressure-flow relationship is linear at physiological pressures such that measures of coronary pressure made at hyperaemia, most often achieved with intravenous adenosine, are proportional to coronary flow (Figure 4).

FFR Calculation

$$\text{FFR}_{\text{myo}} = \frac{P_d - P_v}{R_1} \div \frac{P_a - P_v}{R_2}$$

$$\approx P_d \div P_a \text{ (at hyperaemia)}$$

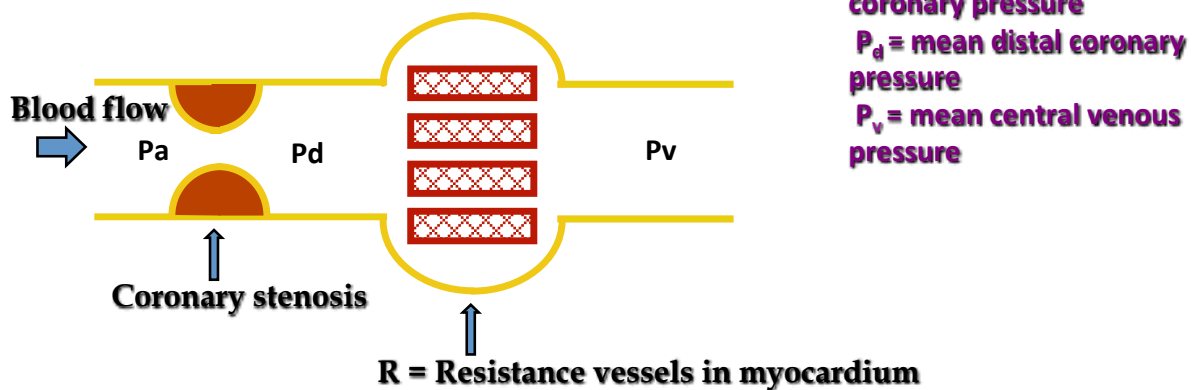


Figure 3: Methodology for FFR calculation

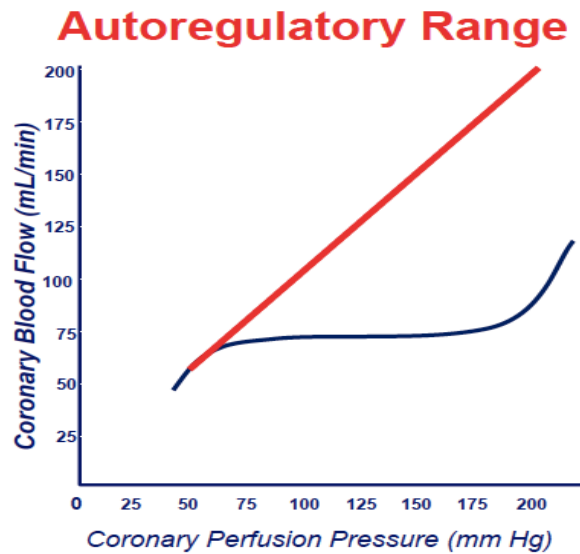


Figure 4: Relationship between coronary flow and Coronary Perfusion Pressure

Central to the calculation of FFR is the ability to measure both pressure proximal to a stenosis (P_a) and pressure distal to a stenosis (P_d) that is achieved with commercially available pressure wires. At hyperaemia, P_a represents myocardial flow in the absence of a stenosis and P_d represents myocardial flow in the presence of a stenosis. FFR is then given as P_d/P_a . An FFR value of 0.5 infers that maximal myocardial blood flow is only 50% of expected and that restoring epicardial patency with revascularisation should improve flow in the territory.

Unlike CFR, FFR has been shown to be a highly reproducible technique. De Bruyne examined the reproducibility of FFR in 13 patients with single vessel disease and normal left ventricular function under differing loading conditions. FFR was relatively insensitive to changes in haemodynamics and contractility with a coefficient of variation of 4.8% as compared with 10.4% (coronary flow reserve) and 27.7% (hyperaemic flow vs. pressure slope index) for other established invasive measures for assessing epicardial stenoses(113).

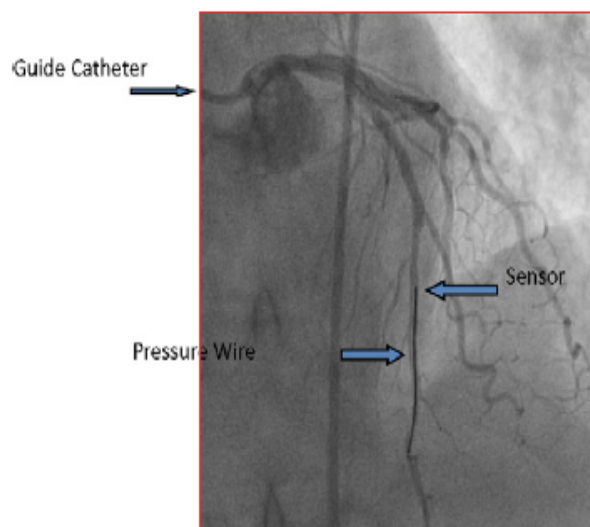
1.5.2 Measuring Fractional Flow Reserve (FFR) in the Cath Lab (Fig 5)

FFR is a simple cath lab based pressure derived index that is easy to perform.

The Technique

Firstly, the coronary artery being studied is engaged with a guiding catheter specific for the arterial system of interest. Diagnostic catheters can be used, but due to potential inaccuracies, it is recommended that a normal guiding catheter be used in order to perform FFR(110). Patients require systemic anticoagulation with intravenous heparin (40–60units/kg) and the use of intracoronary GTN (100–200 mcg) to abolish any residual epicardial vasoconstriction and maintain coronary volume (114). Measurements are performed most commonly with wires that have a pressure sensor at the distal tip. Emerging methods to measure pressure in the coronary artery include the use of fiber-optic sensor technology and these are currently being evaluated in clinically. For standard wires, there is a distal pressure sensor at the junction of the radio- opaque and radiolucent portions of the wire.

Performing FFR



- GTN
- Careful calibration of pressures.

Figure 5: Coronary Angiogram Still frame depicting how to perform FFR

The pressure wire is then calibrated outside of the patient and advanced through the guide catheter and into the artery. Equalization of pressure from the guiding catheter and pressure wire is undertaken prior to the sensor entering the artery. Aortic pressure (Pa) is taken from the guide-catheter and distal pressure (Pd) from the pressure sensor placed beyond the stenosis. The wire itself is a standard 0.014inch wire with similar handling characteristics to conventional angioplasty wires and as such can be used for PCI when necessary.

Induction of maximal hyperaemia through minimisation of coronary resistance is a prerequisite for measurement of FFR. This topic is covered later in the thesis but briefly this is most often achieved with the use of adenosine although papaverine and nitroprusside may also be used. Adenosine can be given as an intracoronary bolus (usually 60–200 mcg) or via an intravenous infusion (140 mcg/kg/min). Continuous monitoring of Pa and Pd is undertaken and FFR is taken as the ratio of hyperaemic Pd/Pa at steady state. The normal FFR value is 1 since the epicardial vessels do not contribute significantly to coronary

Example of FFR

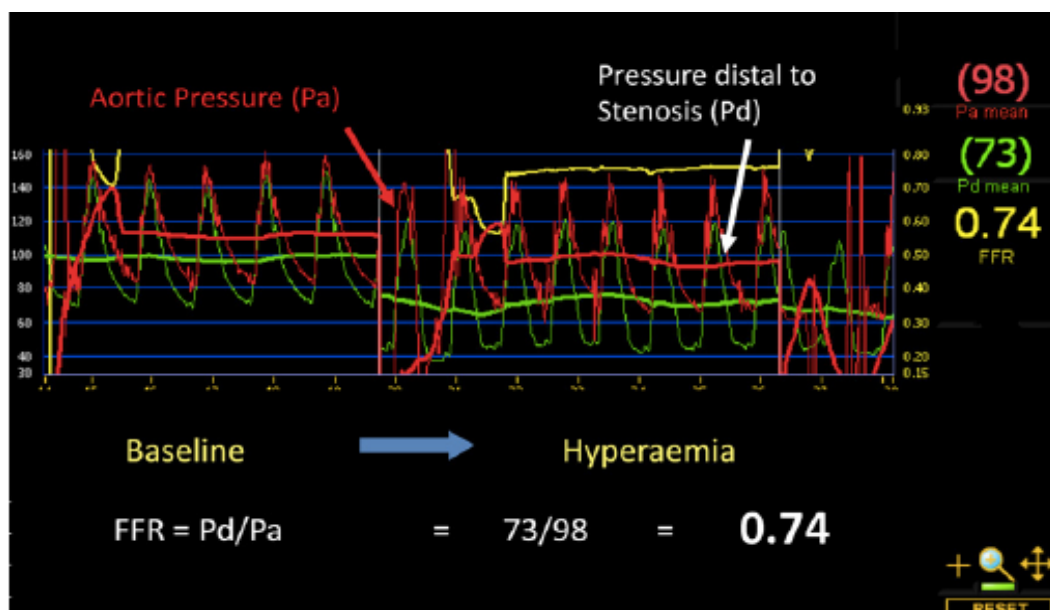


Figure 6: Example of FFR Recording from RadiView

resistance and so aortic pressure is transmitted entirely to the distal vessel (112). Therefore in vessels without stenosis Pa will be equal to Pd. This holds true for all vessels in all patients. Fig. 6 shows an example of an FFR recording.

1.5.2 Validation of Fractional Flow Reserve (FFR)

Following initial exploratory work in animal models (115), numerous clinical studies comparing FFR with non-invasive stress tests established an ischaemic FFR threshold of ≤ 0.75 (116, 117). Pijls and colleagues looked at 41 consecutive patients with an intermediate lesion on coronary angiography and compared FFR with exercise bicycle stress testing, dobutamine stress echocardiography and thallium scintigraphy (116). All patients with an FFR value ≤ 0.75 demonstrated reversible myocardial ischaemia in at least one non-invasive modality. In contrast, 21 of the 24 patients with an FFR ≥ 0.75 had negative testing for reversible ischaemia on all three stress tests. The sensitivity of FFR at predicting reversible ischaemia was 88%, specificity 100% with a positive predictive of 100%, the overall accuracy was 93% (116). Likewise FFR values ≥ 0.80 are associated with negative ischaemic results with a predictive accuracy of 95% (112). Other studies have shown that an FFR value of 0.78 may be more predictive of reversible ischaemia on myocardial perfusion imaging (118). Therefore there is a 'grey zone' of FFR values between 0.75 and 0.80 that produces an area of uncertainty in FFR prediction of reversible ischaemia (110). An important consideration is that the validating studies for FFR were performed in highly selected patients with single vessel coronary artery disease with normal left ventricular function and no previous myocardial infarction. Thus it becomes difficult to extrapolate the validity of FFR outside of these strict parameters to other patient populations e.g. NSTEMI. Recent studies have utilised a cut off value of ≤ 0.8 (119) to determine the physiological importance of a lesion since a proportion of patients with an FFR value between 0.75 and 0.80 who had an

abnormal stress test, normalised following revascularisation. Indeed some authors advocate the use of an FFR cut off of ≤ 0.80 for main epicardial vessels whereby revascularisation may be prognostic and ≤ 0.75 for smaller branch vessels (120). Recent guidelines advise the use of an FFR ≤ 0.8 as an appropriate cut-off value (89).

1.5.3 Use of FFR in patients with NSTEMI: The Ability to Achieve Maximal

Hyperaemia

As already mentioned, FFR is an increasingly important technique to guide revascularisation strategies in patients with stable coronary artery disease undergoing elective PCI. A fundamental aspect of FFR is the ability to achieve maximal hyperaemia in order to achieve a linear relationship between pressure and flow (121).

Maximal coronary hyperaemia is dependent on an intact microcirculation and an adequate hyperaemic stimulus (121). Factors affecting the coronary microcirculation (e.g. severe left ventricular hypertrophy) may impact on the ability to achieve maximal hyperaemia (122). Myocardial infarction (MI) can affect the distal coronary microcirculation secondary to a variety of mechanisms that include distal embolic phenomenon, microvascular stunning and acute ischaemic microvascular dysfunction(123). Due to the heterogeneous nature of MI, this affect may vary according to the size of myocardial infarction and the time from infarction to FFR assessment. Thus the validity of utilizing FFR in patients with recent MI is not fully established.

Although contemporary guidelines incorporate the use of FFR specifically in patients with NSTEMI to guide revascularisation (89) it remains a controversial topic in interventional cardiology (124). Several small studies have shown that FFR assessment is reliable and valid from between 4 and 6 days following the index event (118, 125) and the larger, multinational FAME study also included patients with NSTEMI (126). However

these patients were generally stable without symptoms in the previous 5 days and had unreported infarct sizes. Thus it remains uncertain whether patients with acute NSTEMI can mount a sufficient hyperaemic response to vasodilator stimuli to maintain the diagnostic accuracy of FFR. Furthermore, there is a paucity of data concerning factors involved in determining the hyperaemic response in this population.

1.5.4 Concerns with Using FFR in ACS

The attainment of maximal hyperaemia is based on the assumption of a normal distal microvascular bed. However PET studies have demonstrated impaired microcirculatory function in the infarcted territory compared with healthy controls up to 6 months following AMI(127). Thus in patients with recent MI, microvascular injury, stunning and oedema can result in a failure to achieve minimal resistance and FFR values may be falsely elevated(127).

The effect of acute microcirculatory impairment is exemplified in acute STEMI, a syndrome characterized by distal embolization, inflammation and injury to the microcirculation. Tamita and colleagues described a higher post-PCI FFR in acute STEMI patients compared with stable CHD with similar IVUS parameters. Patients with more pronounced microcirculatory dysfunction as demonstrated by a reduction in TIMI flow (TIMI II) also had a higher FFR compared to those patients with TIMI III flow (128). Furthermore by using a surrogate of a hyperaemic response in 40 patients with acute STEMI, it has been shown that such patients have lowered vasodilatory capacity when compared to stable patients. Intuitively, there was also lower coronary flow reserve and higher IMR in acute STEMI (129). Thus in patients with acute STEMI the assessment of FFR in the culprit vessel is not recommended.

The resistive reserve ratio (RRR) is a measure of the ability to achieve maximal hyperaemia. It is the ratio of basal resistance (BR) to the index of hyperaemic

microcirculatory resistance (IMR). RRR quantifies the response of the coronary microcirculation to hyperaemia (adenosine) and addresses the question of whether or not the corresponding FFR values are accurate. Emerging data suggest this ratio has discriminatory value in patients with stable and unstable coronary disease. A prospective study by our group analyzing RRR in 50 patients with stable angina, 40 patients with acute STEMI and 50 patients within 1-4 days of NSTEMI showed no significant difference between non-culprit vessels in stable angina [2.9 (2.3-3.9)] and either culprit vessels in stable angina [2.8 (1.7-4.8), $p=0.75$] or culprit vessels in NSTEMI [2.46 (1.6- 3.9); $p=0.75$]. RRR was significantly lower in the STEMI patients [1.7 (1.2-2.3)]; $p<0.0001$]. There was no difference in IMR in patients with SA in the non-culprit vs. culprit vessel (16.8 ± 9.1 vs. 18.3 ± 9.2 ; $p=0.44$). However, as expected, IMR was higher and thus microcirculatory function worse in NSTEMI and STEMI compared with the non-culprit SA vessel (NSTEMI, 22.7 ± 11.3 ; $p=0.015$, STEMI, 36.5 ± 35.8 $p<0.0001$)(129).

1.5.5 FFR – Use in late AMI

As the microcirculation recovers, so does the ability to achieve maximal hyperaemia and FFR measurement made at this time point reflect a definitive reduction in perfused myocardium rather than a transient phenomenon. De Bruyne and colleagues highlighted this in 57 patients who were ≥ 6 days after AMI comparing single photon emission computed tomography (SPECT) performed before and after PCI with FFR. They established 100% specificity using an FFR cut off value of 0.75 against truly positive and truly negative SPECT i.e. tests that were positive that reverted to completely negative post PCI (130).

Other groups have shown that rather than recover, the microcirculation remains persistently abnormal in both the culprit and non-culprit territories up to 6 months following myocardial infarction (127). However, this was in a small number of patients and predated

the later FFR threshold studies and thus whilst thought provoking, do not detract from the diagnostic capacity of FFR in chronic MI.

1.5.6 FFR in NSTEMI

Ntalianis et al performed a small prospective cohort analysis on 75 STEMI and 26 NSTEMI patients with non-culprit FFR performed post-PCI to the culprit vessel (131). FFR was repeated at 35 ± 4 days post procedure. There was no significant difference in percentage stenosis or minimal luminal area between studies despite improvements in left ventricular ejection fraction (LVEF). There was also no demonstrable difference in FFR between studies and in only 2 lesions did an FFR >0.80 decrease to <0.75 . The lack of change in FFR was not affected by the improvement in LVEF. This was an important study as it demonstrated that FFR could be used accurately in non-culprit lesions in patients with ACS when measured acutely, important in considering the design of future studies.

The potential clinical utility of using FFR to guide decision-making in NSTEMI was investigated by Carrick and colleagues(82). They performed a retrospective study of 100 patients where FFR was used in the clinical case. The angiograms were analyzed by 5 cardiologists who made an initial treatment decision. Following FFR disclosure the cardiologists were then asked to re-evaluate their original decision. The use of FFR in this manner led to an increase in prescription of medical therapy and improved conformity in decisions amongst cardiologists (82). Potvin et al demonstrated in 201 unselected patients for invasive coronary angiography, the use of an FFR threshold of ≤ 0.75 was safe to allow deferral of stenting. However only 21% of patients had a recent ACS and the use of FFR was neither blinded nor randomized (132).

The only randomized study to date specifically addressing the utility of FFR guided decision-making in NSTEMI was performed by Leesar et al (133). They reviewed the effect

of treatment decisions guided by FFR against stress perfusion scintigraphy. 70 patients with single vessel disease and a history of unstable angina were recruited. There was a significant reduction in duration and cost of index hospitalization in the FFR arm. However, this was not a genuine NSTEMI population with only two-thirds having a diagnosis of AMI, patients were medically stable for 48 hours or more, and the impact of multi-vessel disease was not assessed. Thus although helpful, these studies were in relatively stable patients and not powered to detect any impact of FFR-guided management on health outcomes or to determine the clinical utility of FFR in patients with ACS.

1.5.7 Current FFR Thresholds in NSTEMI

There is currently a lack of data addressing whether the contemporary thresholds for FFR retain their diagnostic accuracy in patients with NSTEMI. Intuitively, the data in STEMI will hold true for NSTEMI yet patients are generally treated within 72 hours of presentation resulting in potential uncertainty. However, there have been several studies that have aimed to establish and validate FFR thresholds for ischaemia in patients with ACS. In 48 stabilised patients with recent MI, Samady and colleagues compared FFR in the infarct related artery to non-invasive findings using SPECT and myocardial contrast echocardiography (MCE)(125). Patients had a mean time to angiography of 3.7 days with 73% of patients with STEMI. The group demonstrated that an FFR ≤ 0.75 had 91% sensitivity, 93% specificity and a diagnostic accuracy of 92% for detecting reversible ischaemia. They provided an optimal cut off FFR value of ≤ 0.78 for detecting reversible ischaemia using ROC analysis. De Bruyne et al demonstrated that an FFR ≤ 0.75 in a culprit vessel ≥ 6 days following an AMI was still predictive of reversible ischaemia shown on non-invasive SPECT imaging(118). Thus, there is some evidence for the use of FFR to determine ischaemia in the culprit territory 4-6 days following ACS. Clearly although the resistance

indices can be higher in NSTEMI it appears that the microcirculation can dilate sufficiently to enable maximal hyperaemia and allow valid FFR measurements.

1.5.8 FFR Guided Decision Making in Patients with UA/NSTEMI

The FAME study showed that in patients with multi-vessel disease there was a 30% reduction in adverse cardiac events (death, MI, target vessel revascularization) with an absolute risk reduction of 5% in the group undergoing FFR guided PCI compared to those undergoing angiographically guided PCI(119). A secondary analysis in 2011 clarified that the benefit observed in the overall trial population was also seen in the UA/NSTEMI group. Overall, FAME included 328 patients with UA/NSTEMI of whom 178 were randomised to angiographically guided PCI and 150 to FFR guided PCI. An absolute reduction in adverse cardiac events of 5.1% was observed in the FFR guided group as well as less contrast useage and on average 1 stent less per patient (1.9 ± 1.5 vs. 2.9 ± 1.1 , $p < 0.01$)(126). However, this was only a subgroup analysis of the larger FAME study with a lack of data on the degree of myocardial injury reported and with patients being stable prior to randomization. Thus there remains an ongoing need for a prospective randomized study to determine the clinical utility of routine FFR use in patients with STEMI.

In a separate observational study of 106 patients with NSTEMI, PCI was deferred as the culprit vessel FFR was >0.75 . The 1 year event rate was 1.9% mortality, 0.9% target vessel revascularisation and 4.7% for readmission with a cardiac cause(134).

1.5.9 Ongoing Clinical Trials of FFR Guided PCI in Patients with ACS

Despite the theoretical considerations outlined above, the weight of evidence suggests that non-culprit FFR can provide useful information regarding functional significance in a high proportion of patients with ACS. On this basis, FFR guided decision making in patients

with STEMI and MVD is now being tested in a series of randomized controlled trials. The COMPARE ACUTE study (NCT01399736) is a randomised controlled trial (RCT) in STEMI patients with MVD in the Netherlands with estimated enrolment of 885 patients divided into immediate FFR guided complete revascularization versus staged non-culprit PCI (ischemia driven) by proven ischemia or recurrent symptoms. The primary endpoint will be a composite of death, non-fatal MI, CVA or revascularization at 12 months and this study is estimated to end in 2018.

The COMPLETE study (Complete vs. Culprit-only Revascularization to Treat Multi-vessel Disease After Primary PCI for STEMI, NCT01740479) is a RCT comparing FFR guided revascularisation within 72hrs of primary PCI versus optimal medical therapy for the endpoint of a composite of cardiovascular death or MI at 4 years. It began recruiting in 2012 and is due to report its findings in 2018.

The Primary PCI in Patients With ST-elevation Myocardial Infarction and Multi-vessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization (PRIMULTI, NCT01960933) study is a RCT of patients with STEMI and MVD with a comparison of the clinical outcome after complete FFR guided revascularisation versus treatment of the infarct-related artery only during primary PCI. The primary outcome is all cause death, MI or revascularization at 48 months. This study, which is based in Denmark, has finished recruiting and is due to report its findings later this year.

However, despite multiple STEMI trials there is a lack of prospective data on the use of FFR in a specific NSTEMI population. In addition, the randomized use of FFR to guide revascularization decisions in the culprit vessel is unknown.

Summary

NSTEMI is the most common cause of myocardial infarction and increasing in

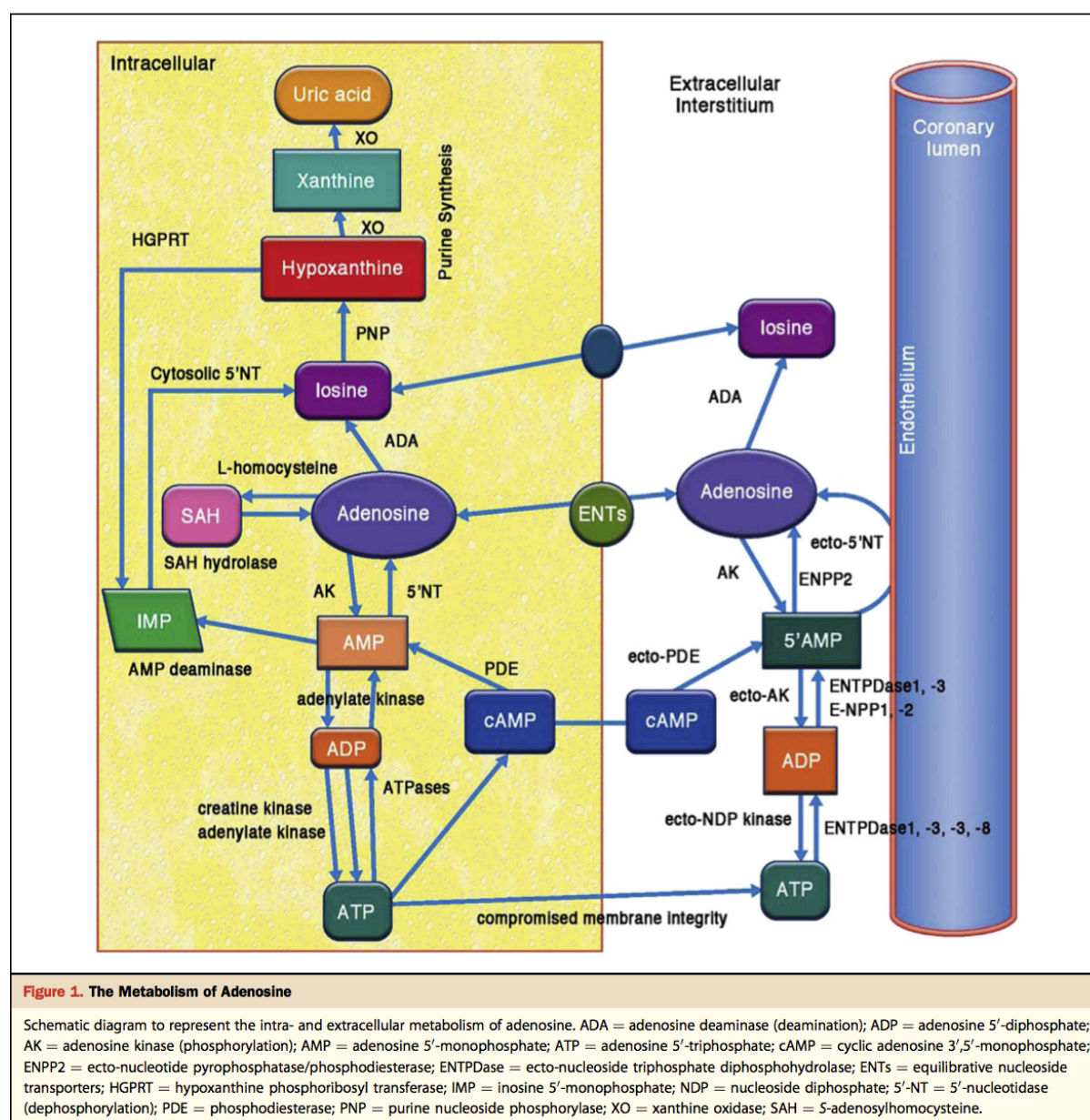
incidence. Amongst high-risk patients undergoing an invasive approach, decision-making is heavily weighted on interpretation of the coronary angiogram. We have learned from IVUS and paradigm-changing clinical trials such as DEFER and FAME that our interpretation of the angiogram is subjective and the ability for cardiologists to predict the haemodynamic importance of a lesion is at best moderate. The use of FFR to guide revascularization decisions has great promise to improve decision-making and perhaps outcomes in patients with NSTEMI by way of reducing unnecessary revascularization. However, to date there is no prospective randomized trial that has focused on higher-risk NSTEMI patients.

1.6 Methods of Achieving Hyperaemia – The Case for Adenosine

Adenosine is a ubiquitous extracellular signalling molecule with essential functions in human physiology. From providing the backbone for basic energy transfer through its adenosine triphosphate (ATP) and adenosine triphosphate interactions to its role in cell signaling, adenosine is a fundamental component of human biology (135). Adenosine has far reaching effects as an extracellular signaling molecule inducing vasodilation in most vascular beds, regulating activity in the sympathetic nervous system, having antithrombotic properties, and reducing blood pressure and heart rate. Such properties are some of the reasons why adenosine and its derivatives have therapeutic effects in most organ systems.

Although adenosine has pleiotropic effects, much of our understanding of adenosine has come through observations of its action in the cardio-vascular system. Pioneering work by Drury and Szent-Gyorgy (136) in the past century pointed to the fact that an adenine compound caused disturbances in heart rate when injected intravenously. It is likely that this adenine compound was in fact adenosine. However, it was not until 60 years later that the use of this property of adenosine was used clinically to treat patients presenting with supraventricular tachycardia (137).

One of the most common reasons for using adenosine in the cardiovascular system is for the production of vasodilation in the coronary microcirculation to produce hyperaemia(121). This property of adenosine to modify microcirculatory function has been used for diagnostic and therapeutic effects for many years and is widely adopted as the reference-standard method of diagnosing ischaemia invasively and noninvasively.



Adenosine is a naturally occurring endogenous purine nucleoside composed of an adenine molecule attached to a ribose sugar moiety(135)(ribofuranose) via a beta-N9-glycosidic bond (6-amino-9-b-D-ribofuranosyl-9-H-purine) (Figure 7). It is the nucleoside base of both ATP and the signalling molecule cyclic adenosine monophosphate (cAMP). Adenosine is rapidly transported into vascular endothelial cells and erythrocytes where it is catabolized by adenosine deaminase to inosine (138). Dipyridamole, a commonly used vasoactive medication(139)exerts its effects through inhibition of adenosine deaminase. Adenosine is (re)phosphorylated by adenine kinase forming adenosine monophosphate, which is incorporated into the high-energy phosphate pool (140). Adenosine levels can rise rapidly in ischaemic tissue due to adenosine kinase inhibition (135).

In the intracellular space, adenosine can be synthesized de novo during purine biosynthesis or accumulate as a result of ATP breakdown. Intracellular adenosine concentrations increase when there is a mismatch between ATP synthesis and use as in ischaemia or hypoxia (141). Adenosine does not freely pass across the cell membrane and requires the use of nucleoside transporters to facilitate the process. Extracellular adenosine arises from active trans- port of intracellular stores or from breakdown of adenine nucleotides outside the cell (135).

Adenosine binds with 4 evolutionary well-conserved receptor subtypes that are ubiquitously expressed: A1, A2A, A2B, and A3 (142, 143). These receptors interact with G-protein receptors. Activation of the G_i protein-bound A1 and A3 receptors reduces adenylyl cyclase activity and decreases intracellular cAMP. Activation of the G_s protein-bound A2A and A2B receptors increases adenylyl cyclase activity and cAMP levels. Adenosine has highest affinity for the A1 and A2a receptors.

Cardiovascular Effects of Adenosine

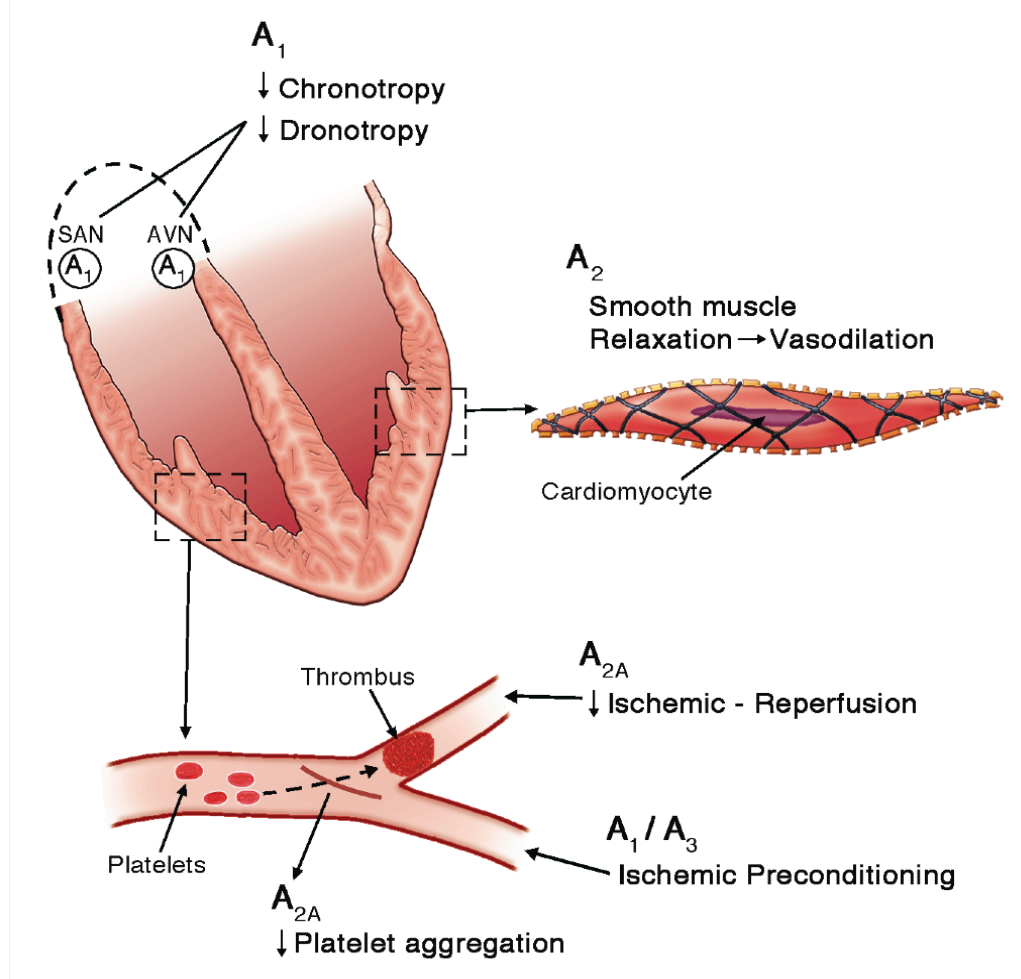


Figure 8: Cardiovascular Effects of Adenosine

Activation of A2A and A2B adenosine receptors produces potent vasodilation of most vascular beds including the coronary circulation, resulting in an increase in myocardial blood flow(144). However, A2A and A2B activation produces vasoconstriction in renal afferent arterioles, splenic arteries, hepatic veins(145).

A1 receptors generally have an inhibitory function on most tissues. Activation of cardiac A1 receptors has a myocardial depressant effect with negative chronotropic and dromotropic effects. A1 receptor activation also mediates inhibition of atrioventricular (AV) node conduction and prolongation of the refractory period via inhibition of cAMP-mediated calcium influx and enhances potassium conduction (146)(Figure 8).

A2A receptor activation also produces anti-inflammatory effects and acts as a major target of caffeine. A2B receptors are found on human mast cells and are thought to produce mast cell degranulation and bronchial constriction (147). A3 receptors are mainly peripherally located but are thought to play a role in mediating pre-conditioning.

The use of adenosine for stress testing and induction of systemic (and coronary) hyperaemia is primarily related to the activation of A2A receptors and the resultant increase in myocardial blood flow.

1.6.2 The Human Coronary Microcirculation and Adenosine

The coronary microcirculation is a key regulator of myocardial blood flow. Through alterations in microvascular resistance, the microcirculation controls the delivery of blood to the myocardium over a wide range of perfusion pressures and myocardial oxygen demand through the process of autoregulation (148). In humans, coronary blood flow can increase up to 5 times the basal flow to meet increased demand (149). Such an increase in blood flow is referred to as a hyperaemic response and in humans is commonly observed in response to ischemia and exercise (150, 151). Quantifying the hyperaemic response is a critical step in

understanding the coronary circulation and is applied in most physiological assessments of myocardial blood flow. Maximal hyperaemia can be achieved through a variety of methods. Exercise is commonly used, but the ability of some patients to exercise is limited. Vessel occlusion to produce ischaemia (152) (and thus reactive hyperaemia) is another method used in animal models but is not practical or safe to be used in humans not undergoing percutaneous coronary intervention (PCI) due to the inherent risk of vessel injury. Pharmacologically induced vasodilation is a commonly used method of achieving hyperaemia in the noninvasive and catheter laboratory settings. Available agents include adenosine, papaverine, sodium nitroprusside, adenosine 5-triphosphate, and dobutamine. Practically, the ideal hyperaemic agent should have a rapid onset of action, short duration of action, low cost with no significant side effects (153). For these reasons, adenosine, administered via either the intracoronary or IV route, has become the most widely used method of achieving hyperaemia in clinical practice.

1.6.3 The Case for Adenosine

Despite extensive use of adenosine in animal experiments, there was some reluctance to use it for interrogating the human coronary circulation due to concerns over hypotension and heart block. However, work performed by Wilson et al. (113, 154) and others demonstrated that the use of adenosine was safe via both the intracoronary and IV routes and that it could reliably induce near-maximal coronary hyperaemia in most patients with little effect on systemic blood pressure. Although it was evident that adenosine produced coronary microcirculatory vasodilation, the exact mechanism of action remained incompletely understood.

1.6.3.1 Functional and anatomic aspects of hyperaemia.

The coronary circulation can be thought of in terms of a 3-compartment model, each of which contributes to the overall resistance to flow. The large epicardial vessels (0.5- to 5.0-mm diameter) make up the first compartment (R1) and divide into progressively smaller branches known as the resistance microvessel (155). This second compartment (R2) consists of small coronary arteries/pre-arterioles (100- to 500- μ m diameter) and arterioles (<100- μ m diameter), which branch into intramyocardial capillaries to create the third compartment (R3). Ultimately, these drain into the coronary venous system (156). Under non-pathological resting conditions, the epicardial vessels offer little resistance to coronary flow, acting as passive conduits only. Approximately 60% of resistance is provided at the arteriolar level, 25% at the capillary level, and the remaining 15% in the venular compartment. During hyperaemia, total resistance decreases across the coronary circulation by 70%. In the arteriolar and venular compartments, resistance decreases by 86% and 98%, respectively, resulting in minimal alteration of capillary hydrostatic pressure such that the capillaries offer the most resistance to coronary blood flow at hyperaemia. Thus, the capillaries provide the ceiling for the hyperaemic response.

Adenosine exerts its predominant vasodilatory effect on coronary microvessels <150 μ m in diameter. Whether this is an endothelium-dependent process is unclear. An intact endothelium is not necessary for an adenosine response *in vitro* (157). However, work performed in humans *in vivo* has demonstrated that the vasodilator effect of adenosine in the forearm can be inhibited by a nitric oxide synthase inhibitor (158).

For the assessment of coronary stenoses, the effect of adenosine on the coronary microcirculation is to produce vasodilation to counteract the influence of autoregulation and ensure that resistance is minimal. In the assessment of fractional flow reserve (FFR), the use of adenosine in this manner allows for a near-linear relationship between pressure and flow to

be achieved. However, in the presence of severe stenoses, some have argued that there is a limited vasodilatory response to adenosine such that basal flow may equal hyperemic flow (159). However, others have shown in animal models that even in the presence of severe stenosis, there exists some retention of vasodilatory capacity of the microcirculation to adenosine (160). Regardless, it is of limited clinical importance because in most catheter laboratory settings, FFR is really only used for intermediate stenoses (40% to 70%).

Adenosine is widely available worldwide and relatively inexpensive, producing stable and reproducible effects, hence, its increasing use in both diagnostic and interventional cardiology over the past 20 years. Furthermore, the availability of pre-made adenosine infusion bags that are stable at room temperature and suitable for short-term storage adds to its appeal (161).

1.6.4 Methods of Administration

The most common method of administration is the IV route frequently used for the termination of AV node-dependent tachycardias and for the attainment of hyperaemia in noninvasive stress testing. In the context of achieving maximal hyperaemia in the catheter laboratory, both the intracoronary (IC) and intravenous (IV) routes are used.

IC adenosine. IC administration of adenosine is simple and quick. Its peak effect occurs <10 seconds after administration, and it has a duration of 20 seconds (162). For this reason, the IC route is not used in cases in which a longer period of steady-state hyperaemia is required such as when performing an FFR pullback or more complex assessments of microvascular function (122). Earlier studies had suggested a maximal IC dose of adenosine of 16 µg for the left coronary artery and 12 µg for the right coronary artery (163) with increasing doses of 2 orders of magnitude to ensure maximal vasodilation(164). These protocols were challenged by animal data suggesting that higher doses of adenosine may be needed to achieve maximal

hyperaemia(165, 166)and clinical studies that suggested that standard adenosine dosing failed to achieve maximal hyperaemia compared with papaverine and IV adenosine(163, 166). Current recommendations for IC adenosine dosing are 100 µg in the right coronary artery and 150 - 200 µg in the left coronary artery, increasing the doses incrementally by 30 µg to a maximum of 200 µg(114).

Whether the IC route is as efficacious at producing maximal hyperaemia compared with the IV route is a controversial area that has been addressed in several clinical studies. The lower efficacy of IC adenosine compared with IV adenosine was highlighted in a study by Casella et al (167). They compared the effects of IC versus IV adenosine in 50 stable patients; 60 mg of adenosine was used with increasing doses up to 150 mg. At the lower, “standard” doses, 10% of vessels with an initial FFR value >0.75 had a subsequent value less than this cutoff point with higher IC doses or IV administration.

Leone et al. (168) also examined the dose-response of IC adenosine compared with IV adenosine. They demonstrated that only the higher doses of IC adenosine (600 µg) produced hyperaemic efficacy similar to that of IV adenosine and that standard dosing (60 to 300 µg) with IC adenosine was not sufficient. Importantly, lower doses of adenosine were associated with inferior diagnostic accuracy compared with IV adenosine. However, at higher doses of IC adenosine, transient AV block developed in nearly 25% of patients.

De Luca et al. (169) demonstrated similar results in 46 patients with intermediate coronary stenoses undergoing diagnostic FFR evaluation. They showed that FFR values progressively decreased with increasing doses of IC adenosine up to 720 µg. With this, the number of patients identified with FFR values <0.75 increased. Of interest, and in contradiction to Leone et al.(168), increasing the adenosine dose did not increase the incidence of side effects, which was very low.

Thus, it appears from studies to date that the IV route of administration has a greater

efficacy for achieving maximal hyperaemia compared with the conventional IC dosing with the added advantage that FFR pullback and more complex physiological assessments can be made. Furthermore, standard adenosine dosing may not be sufficient to produce a hyperaemic response, and higher doses may be required.

1.6.4.1 Central versus peripheral route of administration

Central venous infusion of adenosine through the femoral vein has been the gold-standard method of hyperaemia induction, particularly in the assessment of FFR (116). However, it requires femoral vein access and is inconvenient during transradial catheterization, which is an increasingly preferred method of arterial access. In a study by Seo et al.(170), involving 71 patients, no difference was found in the hyperaemic efficiency of IV administration of adenosine via the forearm compared with the femoral vein. The number of functionally significant stenoses (FFR <0.75) was also not different between the 2 routes, and there was no difference between the hyperaemic mean transit time and index of microcirculatory resistance, suggesting that minimal resistance and thus maximal hyperaemic response was achieved with both routes of administration. Consistent with these findings, De Bruyne et al.(171) showed that the hyperaemic efficacy of adenosine was similar in both central and peripheral venous infusions, and increasing the dose to >140 mg/kg/min did not improve the vasodilatory action of adenosine. In both of these studies, the time to maximal hyperemia was longer with forearm vein infusion of adenosine than with the femoral vein infusion, with a mean difference of 15 seconds, suggesting that when a peripheral venous route is selected, adenosine should be infused for a greater length of time.

In contrast to these findings, Lindstaedt et al.(172) compared the hyperaemic efficacy of adenosine infusion between the femoral vein and the antecubital vein in 50 patients and reported that a 140-mg/kg/min infusion of adenosine via the antecubital vein was slightly less

effective than the femoral vein infusion with a higher frequency of lesion severity underestimation. However, the mean FFR difference between the 2 routes was only 0.013. Of interest, the group administered adenosine at higher doses (170 mg/kg/min) peripherally and found no difference in hyperaemic efficacy compared with the femoral route. For this reason, they recommended administering a higher dose of adenosine via the antecubital vein to achieve hyperaemic efficacy similar to that via the femoral route.

The concept of increasing the dose of adenosine to improve hyperaemic efficacy appears intuitive. However, unlike the findings of Lindstaedt et al.(172)described previously, other groups have not found such a relationship. In 1 study, the addition of an additional IC bolus of adenosine did not result in any change in FFR compared with standard adenosine infusion, although it did increase the incidence of transient AV block (170). These findings were in agreement with other investigators who also showed no evidence of any change in FFR with doses of up to 240 mg/kg/min (171). We recommend the use of IV adenosine at a dose of 140 mg/kg/min and either the peripheral (via a large-caliber vein) or central route depending on operator preference. If using the peripheral route, it may take longer for a hyperaemic response to develop, and thus a longer infusion time may be required. Furthermore, if the FFR is borderline, higher doses of adenosine may be used, but we do not advocate this for all patients.

During the initial phase of adenosine infusion, there can be differential changes to proximal and distal coronary pressure such that the FFR value may fluctuate during this period. This is a critical point because, if FFR values are taken without the attainment of steady-state hyperaemia, the value may be inaccurate and lead to incorrect assumptions regarding the hemodynamic significance of a lesion.

1.6.5 Adenosine in the setting of myocardial infarction and reperfusion

There is a strong body of experimental evidence to suggest that adenosine can protect the myocardium from both ischaemic (173-175) and reperfusion injury via its potent vasodilatory effects and possibly by anti-inflammatory and antiplatelet properties (175, 176). However, clinical studies with adenosine in humans have yielded mixed results. IV adenosine during primary PCI was tested in 2 large randomized trials (177, 178) (AMISTAD I and II, including 218 and 2,118 patients, respectively). Both of these trials demonstrated that adenosine reduced infarct size, but did not reduce the primary clinical endpoint, with in-hospital and 6-month clinical outcome being similar to those in the placebo group. However, in a post-hoc subgroup analysis, a benefit was seen in those receiving reperfusion therapy within 3 hours (179). These data are consistent with the results of a small trial of IC infusion of adenosine in patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary angioplasty, which showed favourable effects on the incidence of no-reflow, left ventricular ejection fraction, and clinical course(180).

Improved myocardial reperfusion, as assessed by ST-segment elevation resolution after primary PCI, was observed in other smaller studies(181, 182). Conversely, a randomized, placebo-controlled trial of 112 patients found no evidence that selective high-dose IC administration of adenosine distal to the occlusion site in the culprit vessel in STEMI patients resulted in any incremental myocardial salvage or reduction in microvascular obstruction (183). In addition, a single-blind study of 448 STEMI patients randomized to 2 bolus injections of IC adenosine (2x120 mg) or matching placebo after manual thrombus aspiration failed to show any difference in the primary endpoint of residual ST-segment elevation after primary PCI(184). Recently, these data were again tested in a randomized study comparing adenosine, sodium nitroprusside, and saline solution. The use of 120 mg of adenosine as a bolus followed by 2 mg administered in 33-ml of saline solution over 2 min as

a slow bolus was associated with improved ST-segment elevation resolution on electrocardiography but not angiographic microvascular obstruction or major adverse cardiac events(185). Despite these mixed findings, IC adenosine is recommended by both the European Society of Cardiology (89) and the American Heart Association (186)guidelines for the treatment of no-reflow.

Pre- and post-conditioning

Transient episodes of ischemia render the myocardium more resistant to subsequent ischemia, a phenomenon known as ischaemic pre-conditioning (187). This effect is thought to be partly mediated by endogenous adenosine. The pre-conditioned state is triggered through activation of A1 and A3 receptors by adenosine before the onset of ischaemia (188, 189). Pre-conditioning has been shown to improve outcomes in patients undergoing coronary artery bypass graft and elective PCI (190). In a small study of 30 patients undergoing PCI, Leesar et al.(191) demonstrated that a 10-min IV adenosine infusion (dose of 2 mg/min) administered before the PCI pre-conditioned the myocardium(191). However, among stable elective patients undergoing PCI, the randomized administration of 120 mg and 180 mg of adenosine into the right and left coronary arteries, respectively, was not associated with a reduction of periprocedural myocardial infarction, Thrombolysis In Myocardial Infarction frame count, or in-hospital death(192).

For obvious reasons, ischemic pre-conditioning is limited to patients who are due to have planned ischemia as in the case of coronary artery bypass graft and PCI.

Post-conditioning refers to a time-sensitive cardioprotective strategy induced by brief repetitive interruptions in blood flow applied immediately at the onset of reperfusion(193). Evidence suggests that, like pre-conditioning, post- conditioning involves endogenous activation of A2a and A3 receptor subtypes. Several small studies on acute STEMI patient

groups have shown a cardioprotective effect of post- conditioning (194). Hahn et al. (195), using a protocol that consisted of 4 cycles of 1 min of balloon inflation followed by 1 min of balloon deflation within 1 min of reflow after coronary stent deployment, demonstrated that patients in the post-conditioning group were found to have 36% smaller infarctions as determined by serum creatine kinase release during the first 72 h of reperfusion and lower peak creatine kinase. However, the recent POST (Ischemic Post- conditioning During Primary Percutaneous Coronary Inter- vention: the Effects of Post- Conditioning on Myocardial Reperfusion in Patients With ST-Segment Elevation Myo- cardiac Infarction) trial in 700 patients undergoing primary PCI demonstrated that ischemic post-conditioning with 4 cycles of 1 min of balloon inflation after restoration of coronary blood flow was not associated with improved myocardial reperfusion.

Adenosine levels can rise rapidly in ischemic tissue due to adenosine kinase inhibition, and this pathway is involved in mediating ischemic pre-conditioning. To date, cyclosporine is the most promising pharmacological post-conditioning mimetic drug(196). Cyclosporine is thought to derive its cardioprotective effects from inhibiting formation of the mitochondrial permeability transition pore, a key component of lethal reperfusion injury. The mitochondrial permeability transition pore appears to form in the early stages of reperfusion in response to the calcium overload and reactive oxygen species generation that develops with reperfusion.

1.6.6 Paroxysmal supraventricular tachycardia.

Therapeutically, IV adenosine in a bolus dose of 6 to 12 mg (or higher) slows AV nodal conduction and by this mechanism interrupts re-entrant pathways involving the AV node and restores sinus rhythm in most patients with supraventricular tachycardia(197). Included in this group are typical AV nodal re-entrant tachycardia, AV reciprocating

tachycardia with a concealed bypass tract, and AV reciprocating tachycardia in Wolff-Parkinson-White syndrome. Diagnostically, by causing transient AV block, adenosine may unmask atrial flutter/atrial fibrillation (AF) and permit the correct diagnosis of broad complex tachycardias(197). Adenosine can also terminate some ventricular tachycardias, particularly those mediated by triggered activity(198).

1.6.7 Safety concerns and side effects of adenosine.

As the half-life of adenosine is brief, both its desired and unwanted effects are generally short lived. Side effects are common with adenosine and reflect the ubiquitous nature of adenosine receptor expression. In general, they are more prevalent with IV than with IC adenosine. In the Adenoscan study, a large multicenter registry with >9,000 patients, examining the safety and tolerability of IV adenosine infusion for stress imaging studies, side effects due to adenosine were reported in 81% of patients(198). Standard IV dosing via a peripheral venous catheter was used. Commonly reported side effects included flushing (36.5%), dyspnoea (35.2%), chest pain (34.6%), gastrointestinal discomfort (14%), and headache (11%). AV block and arrhythmias occurred in 7.6% and 3.3%, respectively. Bronchospasm occurred in 0.1% of the study group. Importantly, there were no deaths in the cohort. Side effects were more common in female patients, younger patients, and those with a higher body mass index. Age older than 70 years was the only independent predictor of AV block after adenosine administration(198). Of note, side effects reported in this study are far higher than those reported in other studies and reflect the fact that the adenosine infusion was continued for 6 minutes, which is longer than is required for invasive physiology protocols.

Furthermore, in a study of 574 patients undergoing cardiac stress magnetic resonance imaging, the incidence of side effects was much lower(199). Chest pain and dyspnoea were reported in only 14% of the patient group, with nausea and vomiting in 5%(199). Adenosine

was infused for only 3 min at 140 mg/kg/min, which could explain the disparate results compared with the previously cited study. The incidence of patient-reported side effects with a novel selective A2 agonist was still 73%, with only a marginal improvement in symptom score when directly compared with adenosine (see later) (200).

In patients with recent unstable coronary disease, non-culprit lesions may be particularly difficult to assess. On the one hand, information from previous stress testing may be lacking, and thus tools such as FFR could be particularly useful; on the other hand, altered hemodynamics during adenosine or side effects may be less well tolerated. However, despite such concerns, the use of adenosine, specifically for patients undergoing comprehensive invasive coronary physiological assessment appears safe(119, 126)

In November 2013 the United States (US) Food and Drug Administration (FDA) issued a safety announcement on the risk of myocardial infarction (MI) and death in patients receiving Adenosine for stress testing. This announcement followed from reports in the FDA Adverse Event Reporting System (FAERS) and medical literature of serious adverse events (SAE) from 1995 to 2013, including 6 cases of MI and 27 cases of death following adenosine administration (typically within 6 hours). Therefore despite a large body of evidence in the established literature demonstrating clear safety of adenosine there remain concerns with its ongoing safety both in the office base and amongst higher acuity patients.

1.6.7.1 Arrhythmias.

Adenosine has proarrhythmic potential. AF is well recognized(201)and in some reports is the most common arrhythmia (2.7% after IV administration)(201). Adenosine is thought to provoke AF through shortening of the atrial action potential duration. Its incidence varies depending on the population being studied. For example, in patients with known conductive system disease undergoing electrophysiological assessment, the incidence of AF

was 12%. However, it is a rare occurrence in the catheter laboratory and in noninvasive assessments (202). In a retrospective dataset of 1,948 patients undergoing adenosine stress myocardial perfusion studies, the incidence of AF was 0.41% (203). AF was usually preceded by either increasing atrial ectopy or significant bradycardia. When AF occurs, it is usually well tolerated unless associated with an accessory pathway, where it may produce unstable arrhythmias requiring direct current cardioversion (204).

Ventricular arrhythmias have also been reported with adenosine. This is usually as a consequence of adenosine-induced bradycardia and is more likely to occur in patients with a propensity for bradycardia-related arrhythmias such as those with a prolonged QTc interval (205).

The main contraindications to the use of adenosine infusion are documented allergy to adenosine or severe asthma. Inhaled adenosine monophosphate and ATP are known to cause bronchospasm in asthmatics, most likely a result of mast-cell mediator release(206). Despite case reports of bronchospasm developing in asthmatic patients after adenosine(207), these instances are very rare, and such an entity requires distinguishing from the more frequently encountered occurrence of benign dyspnoea. Adenosine causes a sensation of dyspnoea in healthy patients but has not been shown to objectively produce bronchospasm (208). This dyspnoegenic property has been proposed to be a result of direct stimulation of pulmonary C fibers by adenosine (208). In patients with mild to moderate persistent asthma, the IV infusion of adenosine did not cause any significant change in lung function compared with placebo and healthy control groups. However, asthmatic patients had a greater intensity of dyspnoea in response to adenosine. Thus, the use of IV adenosine in well-controlled, mild to moderate asthma appears to be safe.

The presence of chronic obstructive pulmonary disease has also been suggested as a contraindication to adenosine use, but we and others believe that the use of IV adenosine for

mild to moderate airway disease, is safe (121). If chronic obstructive pulmonary disease severity is a major concern, then IC adenosine or an alternate agent can be used. When using the IC route, bradycardia/transient AV block may be observed, particularly at higher doses and when administering into the right coronary artery (114). In most reported cohorts, the incidence varies from 0%(163)to 16%(168) with standard dosing.

1.6.7.2 Adenosine Interactions

Experimental data have confirmed that methylxanthines can cause an attenuated hyperaemic response through blockade of arteriolar A2a receptors(209). Caffeine (1,3,7 trimethylxanthine) is thought to competitively inhibit the adenosine receptor and thus may also attenuate the hyperaemic response(210). This has been highlighted in animal studies in which caffeine led to a blunted hyperaemic vasodilator response (211). One study suggested that increasing the adenosine dose to 210 mg/kg/min abolished any caffeine effect (212). Some earlier studies failed to show this relationship between caffeine and the hyperaemic response, but such studies tended to have lower caffeine concentrations (213). Caffeine appears to have a dose-dependent affinity for the adenosine receptor, and this may explain these discordant findings. Theophylline, a xanthine derivative commonly prescribed for reactive airway disease also antagonizes adenosine and may need to be withheld before any imaging/invasive assessment. We advocate the avoidance of caffeine for at least 12 hours in patients undergoing stress perfusion imaging or invasive coronary flow assessment if adenosine is the hyperaemic agent to be used. Furthermore, a full drug history should be taken to make sure that there are no potential interactions that could affect the hyperaemic response. Aminophylline and theophylline, both nonselective adenosine antagonists, may be used in situations where the effect of adenosine requires reversal. However, due to the short half-life of adenosine, this is rarely required in a catheter laboratory setting but is often used

in myocardial perfusion imaging where the longer acting dipyridamole is used.

1.6.8 Novel Agents for Achieving Hyperaemia

In addition to the agents that we have already mentioned, there are new agents available to achieve hyperaemia. Regadenoson is a selective adenosine A2a receptor agonist and in theory should produce hyperaemic effects similar to those of adenosine without the additional side effects often seen with A1, A2b, and A3 receptor activation(214). It is administered as an IV bolus and, because of its longer half-life compared with adenosine (2 to 3 min), has a longer duration of action. Importantly, there is similar efficacy in terms of the time taken to achieve hyperaemia compared with adenosine(214). Regadenoson produces blood pressure-lowering effects similar to adenosine but causes a significantly higher heart rate response. The adoption of regadenoson for perfusion imaging followed 2 large randomized studies showing that it produced diagnostic information similar to that of a standard adenosine infusion (200, 215). Furthermore, although side effects were common, they appeared to be fewer than those reported in patients receiving adenosine. Because of its A2a receptor selectivity, regadenoson appears to be safe in patients with mild asthma (216). However, as yet there is a lack of data to support its use in more severe forms of airway obstruction.

Arumugham et al. (217)compared regadenoson with adenosine for the assessment of FFR in 20 patients with intermediate coronary stenoses and showed an excellent correlation between the 2 drugs ($r = 0.93$, $p < 0.0001$). Furthermore, the minimal value of FFR appeared to be achieved earlier with regadenoson compared with adenosine. More recently, Prasad et al. (218)demonstrated that in 57 patients undergoing clinically indicated FFR assessment in the catheter laboratory, regadenoson was as efficacious as adenosine for inducing hyperaemia, with the FFR in both groups being 0.79. There were fewer (but not statistically

significantly fewer) side effects with regadenoson, and the nadir to hyperaemia was shorter in the regadenoson group.

Nicorandil, a drug with nitrate-like effects through its increase in cyclic guanosine monophosphate and also K^{β} ATP channel modulation, was also compared with adenosine in 210 patients with an intermediate coronary stenosis(219). Hyperaemic efficacy was compared with IC and IV adenosine versus IC nicorandil. The investigators found that the hyperaemic efficacy of IC nicorandil (2 mg) was non-inferior to that of IV adenosine. There was also no significant difference between the index of microvascular resistance with IV adenosine compared with IC nicorandil, suggesting that similar levels of steady-state minimal resistance were obtained with both drugs. Moreover, there were no side effects/adverse reactions with nicorandil, whereas with adenosine, AV block occurred in 12 patients with IC administration and 4 patients with the IV administration (219).

Summary

Adenosine has a critical role in the noninvasive and invasive assessment of myocardial perfusion as well as having therapeutic efficacy in patients with no-reflow. In the electro- physiological setting, it has an important role in both the diagnosis and treatment of a range of arrhythmias. Although side effects are frequently reported, they are seldom troublesome and due to the short half-life of the drug are transient. The recently published FDA concern for stress testing using adenosine is unexpected given the wealth of evidence in support of safety. However, more data on adenosine safety is required. Newer agents show promise and may attenuate concerns regarding adenosine use but require further data before they replace adenosine as a first-line agent.

Aims of Thesis

1. To assess the clinical utility and difference in health outcomes using fractional flow reserve in patients with NSTEMI compared with angiographic guided management.
2. To assess the relationship between the visual angiographic severity of coronary artery stenosis and haemodynamic severity as defined by FFR amongst patients with NSTEMI
3. To assess the accuracy of fractional flow reserve for predicting perfusion defects on stress perfusion CMR amongst patients with recent NSTEMI
4. To compare the utility of differing oedema imaging methods in patients with NSTEMI
5. To assess the safety of adenosine and coronary pressure wires in patients with recent acute coronary syndromes.

Methods

Due to the heterogeneity of studies involved in this thesis, the main methods for each study are presented in the individual results chapters. Below is a broad overview of the main methods for the thesis.

2.1 FAMOUS-NSTEMI Study

2.1.2 Setting and Design.

A prospective multicenter parallel-group 1:1 randomized controlled superiority trial was conducted across 6 UK centers including 3 academic cardiothoracic centers and 3 nonacademic regional hospitals: West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Glasgow, UK; University Hospital Southampton, Southampton, UK; Hairmyres Hospital, East Kilbride, UK; Royal Blackburn Hospital, Blackburn, UK; Freeman Hospital, Newcastle, UK; City Hospitals Sunderland NHS Foundation Trust, Sunderland, UK. The first patient was randomized on October 25, 2011; and the trial completed follow-up in November 2013. An overview of the key trial timelines is provided in figure 9.

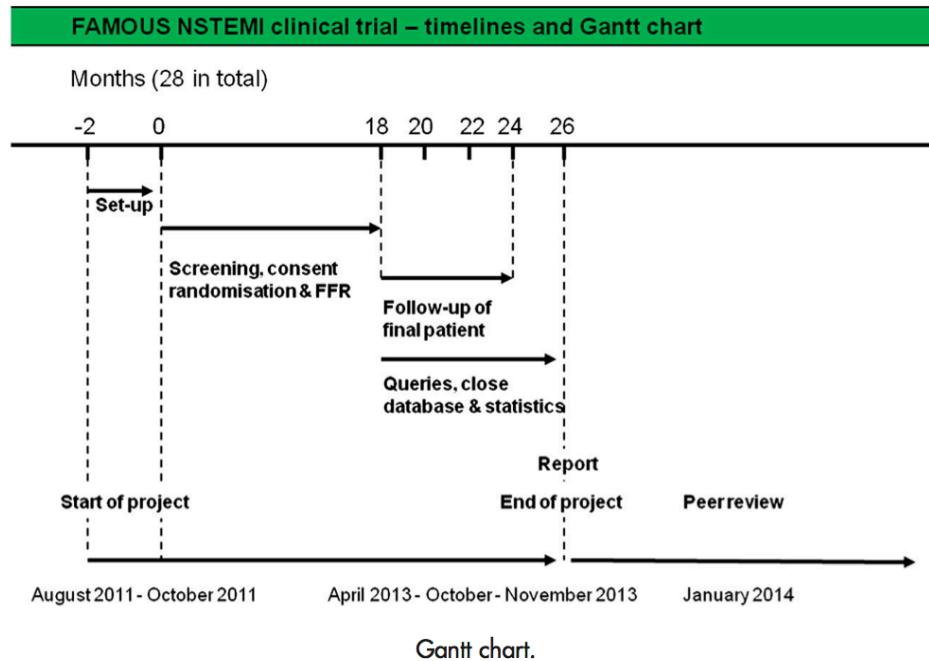


Figure 9: Gantt Chart for FAMOUS NSTEMI study

2.1.3 Consent

Patients were consented on the ward either the day before or on the morning of their coronary angiogram. Patients were provided with an information sheet explaining the nature of the study and the potential risks involved. They were given sufficient time to read the information sheet before myself or one of the research nurses went back to answer any questions the patient may have regarding the study. If the patient was happy then consent was taken, if not then the patient was thanked for considering and the screening data recorded.

2.1.4 Study population.

Consecutive NSTEMI patients with a clinical diagnosis of confirmed or suspected type 1 MI were screened before coronary angiography. A NSTEMI was defined according to the occurrence of acute ischemic symptoms (e.g., chest discomfort) and elevated cardiac biomarkers but without ST-segment elevation on the electrocardiogram. Type 1 represents spontaneous MI due to a reduction in myocardial blood flow secondary to atherosclerotic

plaque rupture and/or coronary thrombosis in one or more arteries. To be eligible for the study patients had to have a clinical diagnosis of recent NSTEMI and at least one risk factor for coronary artery disease (e.g. diabetes mellitus); urgent invasive management planned within 72 hours of the index episode of myocardial ischaemia or a history of recurrent ischaemic symptoms within 5 days. The main exclusion criteria were the presence of ischaemic symptoms that were not controlled by medical therapy, haemodynamic instability, MI with persistent ST elevation, intolerance to anti-platelet drugs, ineligible for coronary revascularisation, a treatment plan for non-coronary heart surgery (e.g. valve surgery), a history of prior CABG, angiographic evidence of severe (e.g. diffuse calcification) or mild (< 30% severity) coronary disease, a life expectancy < 1 year and an inability to give informed consent (Table1).

Patients who gave informed consent but who were not randomized were included in a registry. The reasons for exclusion from the trial after consent but before randomization (e.g., coronary angiogram findings) and inclusion in the registry were prospectively recorded. We aimed to maximize participant retention and follow-up through telephone contact and use of national electronic databases for long-term follow-up.

Table 1: Inclusion and Exclusion Criteria for FAMOUS NSTEMI

Table. FAMOUS NSTEMI study design
Inclusion criteria
Medically stabilized NSTEMI with an elevated troponin (>upper limit of normal for local reference range) with ≥ 1 risk factor for CAD (eg, diabetes, age >65 y, prior CAD, prior peripheral vascular disease, hypertension, hyperlipidemia, family history of CAD)
≥ 1 noncritical coronary stenosis $\geq 30\%$ severity with normal coronary blood flow (Thrombolysis in Myocardial Infarction grade III) in which FFR measurement might have diagnostic value
Invasive management within 72 h of hospital admission or a history of recurrent ischemic symptoms within 5 d
Exclusion criteria
Ongoing ischemic symptoms not controlled by medical therapy
Cardiogenic shock or hemodynamic instability
Angiographic exclusion: highly tortuous or calcified arteries, left main stenosis $>80\%$ (ie, consistent with severe left main disease)
Life expectancy of <1 y
MI with persistent ST elevation
Intolerance to antiplatelet drugs
Unsuitable for either PCI or CABG on clinical or angiographic grounds
CAD $<30\%$ reference vessel diameter
Noncoronary cardiac surgery (eg, an indication for concomitant valve repair or replacement)
Inability to give informed consent
Age <18 y (no upper age limit)

Once the coronary angiogram has been obtained, the cardiologist assessed whether or not the patient was eligible to be randomized based on angiographic criteria (Table 1). The main angiographic inclusion criterion is the presence of one or more non-critical coronary stenoses $\geq 30\%$ severity which are associated with (1) normal coronary blood flow (i.e. TIMI grade III), (2) amenable to revascularization by PCI or CABG and (3) FFR measurement is feasible and may have diagnostic value. A minimum stenosis severity of 30% is adopted for FFR measurement in our study because visual assessment of the angiogram may underestimate stenosis severity. Inclusion of a more severe stenosis (e.g. $>90\%$ severity) is permissible provided the cardiologist believes FFR has the potential to influence the treatment decision based on coronary and patient characteristics. We included patients with left main stem disease, however, if visually it was thought that disease was critical (i.e. $>80\%$), then these patients were excluded. The pressure wire (Certus, St Jude Medical,

Uppsala) will be used in all patients to provide an FFR value across all coronary narrowings $\geq 30\%$ severity as appropriate. Our aim is to maximize inclusion of eligible patients to minimize selection bias.

Once the coronary angiogram was obtained, the cardiologist established an intended treatment plan based on all of the available clinical information and the angiographic findings. The cardiologist's interpretation of the diagnostic angiogram and the treatment plan was then recorded at that time in the catheter laboratory. Therefore, the initial treatment decision was established before randomization or treatment group assignment was known and before the pressure wire was passed into the coronary arteries. Therefore, no FFR measurements were acquired before randomization.

2.1.5 FFR Measurement

FFR was measured according to best practice as described in contemporary guidelines(114). The cardiologist passed the pressure wire across the target coronary stenosis and it was calibrated initially to ensure standardized measurements. When the radio-opaque marker was positioned at the distal end of the guide catheter the pressure wire recording was equalized with the aortic pressure. The wire was then passed into the coronary artery of interest and advanced at least 6 cm distal to the coronary stenosis using standard techniques. Once the marker was appropriately positioned and after an initial 2 minute rest period, an intravenous infusion of adenosine ($140 \mu\text{g/kg/min}$ – $210 \mu\text{g/kg/min}$) via a central vein or large antecubital vein was started to establish coronary hyperaemia. *Typical changes in blood pressure (i.e. fall in systolic pressure $>10\%$), heart rate (i.e. rise in heart rate $>20\%$) and symptoms will be recorded prospectively to confirm a hemodynamic response to adenosine during a period of at least 2 minutes. When there is an inadequate response with the standard dose of adenosine ($140 \mu\text{g/kg/min}$) then the dose was increased up to 210 mcg/kg/min in order*

to best ensure maximal hyperaemia. *If intravenous adenosine was not tolerated then intracoronary adenosine could be administered.*

All patients received an initial intravenous bolus of 5000 units of unfractionated heparin with additional bolus as required to maintain an activated clotting time of 250 seconds. All patients had been pre-treated with aspirin and clopidogrel. A 6F coronary guiding catheter was used routinely and 200 µg of intracoronary nitroglycerin was administered during left and right coronary angiography.

Myocardial FFR was taken as the ratio of distal coronary to proximal aortic pressure during steady state hyperaemia. An $FFR \leq 0.8$ was used as a measure of stenosis significance. In order to facilitate the inclusion of patients with complex disease, an FFR of 0.5 was assigned without requirement to pass the pressure wire in occluded/sub-totally occluded arteries, left main lesions >80% and critical severe epicardial coronary lesions (e.g. >95% severity). This approach is intended to facilitate and maximise the inclusion of all eligible patients(220). According to eligibility criteria in the protocol, FFR was measured in all coronary arteries with one or more stenoses $\geq 30\%$ of the reference vessel diameter based on visual assessment of the angiogram, with normal coronary blood flow (TIMI grade III) and in the opinion of the attending cardiologist FFR measurement will be feasible and may have diagnostic value.

2.1.6 Randomisation.

Once the coronary angiographic findings and treatment plan were recorded and if, in the opinion of the treating cardiologist, the patient remained eligible to continue in the study, randomization was then performed. Randomization took place immediately in the catheter laboratory using a web-based computer randomisation tool provided by the independent Clinical Trials Unit. The randomization sequence was created using the method of randomized permuted blocks.

Patients who gave informed consent but who are not randomised were included in a registry. The reasons for exclusion from the trial after consent but before randomisation (e.g. coronary angiogram findings) and inclusion in the registry were prospectively recorded. Age and sex were recorded in all of the registry participants, and other clinical data were collected wherever possible.

2.1.7 FFR-guided group

Fractional flow reserve was measured by the cardiologist immediately after randomization, and the FFR result was used to guide treatment decisions based on a threshold of 0.80. An $\text{FFR} \leq 0.80$ resulted in a treatment decision for revascularization by PCI or CABG combined with optimal medical therapy; and an $\text{FFR} \geq 0.80$ resulted in treatment with optimal medical therapy alone, in line with contemporary guidelines for optimal secondary prevention drug therapies, cardiac rehabilitation, and risk factor modification. Any changes in treatment following FFR disclosure compared with the initial treatment plan prior to FFR disclosure were recorded.

2.1.8 Angiography-Guided Group and Blinding

In those patients randomized to the angiographic-guided arm, FFR was still measured in all vessels with at least a 30% stenosis. However, the treating cardiologist was not privy to the FFR results. The RadiAnalyzer Xpress (St Jude Medical) was turned out of view by the research team such that it was impossible for the clinical team to see the pressure wire recording. The pressure wire recording was not displayed on any other monitor in the catheter laboratory, and the clinicians and patients did not know the results. When the coronary pressure display was out of view of the clinical team, the cardiologist measured FFR as described above, guided by the research staff who monitored and recorded the pressure wire

data. Therefore, the patient and the clinical team responsible for the patient, including the interventional cardiologists and nurses, were blinded to the pressure wire recording. Quality control checks, including assessments of equalized pressure recordings and verification of symptoms and hemodynamic changes with intravenous adenosine, were conducted in the usual way, with the guidance of the unblinded research team. These steps were followed for all FFR measurements.

2.1.9 Standard care of NSTEMI patients in the National Health Service

The participating hospitals adhere to current guidelines for optimal medical therapy and optimal revascularisation (23). Oral dual anti-platelet therapy and other secondary prevention therapies were recommended in all participants once the diagnosis of NSTEMI had been confirmed. Intravenous nitrate therapy was recommended for patients whose symptoms were not initially controlled by oral anti-ischaemic drug therapy.

In this study, a diseased artery was defined as an epicardial artery with one or more lesions $\geq 30\%$ of the reference vessel diameter and amenable to PCI or CABG. An angiographically significant artery was defined as an artery with one or more lesions $\geq 50\%$ of the reference vessel diameter. A left main stenosis of $\geq 50\%$ and an epicardial coronary stenosis $>70\%$ are usually taken to be obstructive lesions for which revascularization should be considered(89). Patients who were considered candidates for CABG were discussed at the Multidisciplinary Heart Team meeting in each centre. *In the angiography-guided group, the FFR data were not disclosed at this meeting.* If staged PCI was planned then the second procedure was recommended to take place during the index hospitalisation.

The radial artery is the standard route for invasive angiography and PCI in our hospitals and the radial artery was used according to operator and patient preference. Arterial blood pressure and the ECG were monitored in the Cardiac Catheter Laboratory and

cardiology ward. Drug eluting or bare metal stents were used according to operator judgement and in line with clinical guidelines. After the index invasive procedure was completed the patients returned to the cardiology ward and were treated with optimal secondary prevention measures.

2.1.10 Trial Management

The initial treatment decision was prospectively recorded before randomisation and any change to this decision after randomization, such as after FFR disclosure in the FFR-guided group was recorded prospectively in the catheter laboratory during the procedure. At this time, the protocol also required prospective confirmation that in the 'angiography-guided control group', the clinical team were blinded to the pressure wire recordings and FFR values throughout. The investigator was also required to confirm that the protocol was preserved. Adherence to the blinding protocol was monitored with site visits performed by the trial coordinator (Dr Jamie Layland).

The trial was conducted in line with Guidelines for Good Clinical Practice (GCP) in Clinical Trials. Trial management included a Trial Management Group (TMG), Trial Steering Committee (TSC), Clinical Event Committee (CEC), and Data and Safety Monitoring Board (DSMB). Day to day study activity was coordinated by the TMG, which were responsible to the TSC. The TSC were responsible for overall trial supervision. In order to adjudicate and validate adverse clinical events, source clinical data were reviewed by an independent CEC comprised of at least 3 cardiologists. The DSMB followed an agreed charter prepared according to the DAMOCLES guidelines (221). The DSMB had access to unblinded data including the FFR results. The DSMB included one interventional and one non-interventional cardiologist and a biostatistician (Chair), not affiliated to any of the institutions involved in the study and therefore independent of the study team. Progression during the study required

approval from the DSMB after the 35th randomized patient.

2.1.11 Primary outcome

The between-group difference in the proportion of patients allocated to medical therapy only instead of revascularization at baseline. The treatment decision was made by the clinical team in the cardiac catheter laboratory during the index procedure or shortly afterward during the index hospitalisation including when a multidisciplinary heart team review was indicated.

2.1.12 Secondary outcomes

- . 1) The safety and feasibility of routine FFR measurement in NSTEMI;
- . 2) The percentage rate of discordance between an $\text{FFR} \leq$ or ≥ 0.80 and coronary stenosis severity;
- . 3) Major adverse cardiac events are defined as cardiac death or hospitalization for MI or heart failure after randomization. Therefore, emphasis has been placed on “spontaneous” “hard” outcomes. Because the decision for revascularisation may be susceptible to bias, this event is not included in the primary outcome. Information on hospitalisations for other adverse events (i.e., unstable angina, renal failure, stroke, PCI, CABG) was prospectively recorded.
- . 4) Health care costs (including revascularisation procedures, stents, bed days) were prospectively recorded for the index and any subsequent hospitalizations.
- . 5) Quality of life (EuroQoL, EQ-5D). All patients were asked to complete an EQ-5D form at Baseline and at follow up (minimum 6 months).

2.1.13 Health status and frailty

Health-related quality of life (HRQoL; EuroQol 5-Dimensions 3-Level (EQ-5D-3L) was assessed at baseline and again at 6 and 12 months. The participants were interviewed by the research nurses and provided responses for the EQ-5D-3L questionnaire and EQ visual analog scale (EQ-VAS). The EQ-5D-3L questionnaire comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The EQ-VAS records the respondent's self-rated health on a vertical, visual analogue scale where the outcomes are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

Frailty was assessed using the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale(222).

1 Very fit – robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age

2 Well – without active disease, but less fit than people in category 1.

3 Well, with treated co-morbid disease – disease symptoms are well controlled compared with those in category 4.

4 Apparently vulnerable – although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms.

5 Mildly frail – with limited dependence on others for instrumental activities of daily living.

6 Moderately frail – help is needed with both instrumental and non-instrumental activities of daily living.

7 Severely frail – completely dependent on others for the activities of daily living, or terminally ill.

These scores were summarised into 3 groups: Well (scores 1-3), Vulnerable (score 4) and Frail (scores 5 - 7).

2.1.14 ECG analysis

A 12 lead electrocardiogram (ECG) was obtained in all participants following admission to hospital. The ECGs were recorded at 100 Hz and 25 mm/s with an amplitude of 10.0 mm/mV. The ECGs were de-identified, scanned and sent to the lead site for central analysis.

A physician (M.L.) who was blind to treatment group assignment analysed the ECGs for evidence of ischaemia. M.L. had been trained in the University of Glasgow ECG Core Laboratory that is certified to ISO 9001: 2008 standards as a UKAS Accredited Organisation. The ECG criteria for ischaemia were ST-segment depression ≥ 0.1 mV in two contiguous lead. Global ischaemia was taken to represent ≥ 6 leads with ST depression, maximally in V4 and with accompanying T-wave inversion in these leads. Transient ST-segment elevation was taken to represent new ST elevation at the J point in two contiguous leads (≥ 0.1 mV in all leads other than leads V2–V3 where ≥ 0.2 mV in men ≥ 40 years; ≥ 0.25 mV in women < 40 years). The criteria were similar to those used in the TIMACS trial.(223)

2.1.15 Biochemical assessment of infarct size

Troponin I or T were measured as a biochemical measure of infarct size. Blood samples were obtained on admission to hospital before enrolment, at the start of the procedure and 12 - 24 hours afterwards. Different troponin assays were used in each hospital. Troponin T (Elecsys Troponin T, Roche) was measured in patients treated in the Golden Jubilee National Hospital, Hairmyres Hospital, Freeman Hospital and Sunderland City Hospital. A troponin T concentration of 14.0 pg/ml corresponds to the 99th percentile of a

reference population for this assay. Troponin I (Abbott Architect) was measured in patients admitted to acute hospitals in Glasgow. The upper limit of normal for this assay is 0.04 µg/L. In the Royal Blackburn Hospital, troponin I was measured with the high-sensitivity Siemens assay and the upper limit of normal for this assay was < 30 ng/L. In Southampton University Hospital, troponin I was measured (Beckman Coulter Dxi 800) and the upper limit of normal was 0.07 µg/L.

2.1.16 Statistical methods

Analyses will be carried out with R for Windows v3.0.0, SAS for Windows v9.2. The numbers of patients randomised, and the numbers and percentages providing data at each follow-up point will be presented. The number and percentage who withdrew from the study will be presented, and the reasons for withdrawal summarized

The following baseline characteristics will be summarised:

- age (years), sex, ethnic group (white/other), smoking;
- history of cardiac arrhythmia, history of treated hypercholesterolemia, history of hypertension, history of renal impairment, family history of CAD, diabetes mellitus, objective evidence of ischaemia, previous diagnostic angiogram, previous PCI, previous MI, history of congestive cardiac failure;
- current CCS Angina class, current NYHA functional class, Killip class, GRACE score, ejection fraction;
- medications at the time of angiogram (aspirin, anti-platelet, statin, other lipid lowering drug, beta blocker, calcium channel blocker, long acting nitrate, nicorandil, ACE inhibitor, angiotensin receptor blocker, alpha blocker, diuretic, other cardiac medication;
- time from index event to procedure (<5 days or ≥5 days).

Vessels Affected (separate summaries to be provided for all vessels, culprit vessels only, non-culprit vessels only):

- whether each vessel affected (RCA prox, RCA mid, RCA distal, PDA from RCA, Post-lat from RCA, left main stem, LAD prox, LAD mid, LAD distal, 1st diagonal, 2nd diagonal, Cx prox, OM, Cx distal, Post-lat from Cx, PDA from Cx, Additional OM, Intermediate);
- the level of stenosis, and whether each vessel affected with severe stenosis ($>70\%$ or $>50\%$ for the left main stem);
- the FFR value, and whether each vessel affected with $\text{FFR} < 0.80$;
- number of vessels affected;
- number of vessels affected with severe stenosis;
- number of vessels affected with $\text{FFR} < 0.80$;
- maximum stenosis of affected vessels;
- minimum FFR of affected vessels.

With 322 randomized subjects (161 subjects in the FFR disclosed and non-disclosed groups), the study will have 90% power at a 5% level of significance to detect a 50% relative increase in the proportion of patients assigned to medical treatment in the disclosure group from about 15% to 30%. This difference is based on observations made in a pilot study⁽⁸²⁾ performed to inform the design of the current trial. We have assumed zero loss to follow up since the primary outcome is measured during the initial procedure. Allowing for any technical difficulties or loss of data at the time of the procedure the total sample size will be 350 patients (Figure 10).

We anticipated approximately 1400 patients will be screened and 350 patients will be randomized in <2 years. We thought that potentially 25% of screened patients may be

ineligible (e.g. unsuitable for PCI or CABG). Furthermore, a minority of patients may not wish to take part (~25%) and following initial angiography a further 25% may be ineligible based on coronary anatomy and disease resulting in 350 randomised patients. We anticipated the rate of major adverse cardiac events in the control group will be ~20% during ~1.5 years mean follow-up (or at least 35 events in 175 patients) such that the relationship between FFR and cardiac outcome in NSTEMI can be evaluated. The Glasgow Clinical Trials Unit (Robertson Centre for Biostatistics) acted as an independent coordinating center for data management and will conduct the statistical analyses.

The primary outcome of the between group difference in the proportions of patients allocated to medical therapy will be assessed using Fisher's Exact test and the differences in proportions estimated with a 95% confidence interval. Secondary outcomes will also be recorded. Clinical event rates will be presented for each follow up assessment point and compared between groups using the same methods as the primary outcome. Clinical events of interest (as determined by the Clinical Events Committee) will be:

1. Major Adverse Cardiovascular Events (MACE) – the composite of cardiovascular death, non-fatal MI, unplanned hospitalisation for TIA or stroke;
2. Major Adverse Cardiac Events – cardiac death, non-fatal MI or unplanned hospitalisation for heart failure;
3. Death from any cause.

The rate of discordance between FFR and coronary stenosis severity assessments will be estimated over all patients and segments and a 95% confidence intervals calculated taking into account the within subject clustering. For both randomised groups combined, scatterplots will be produced showing the FFR value vs. the level of stenosis, overall and for culprit/non-culprit vessels separately. The rate of discordance between FFR and visual assessment of coronary stenosis severity will be presented.

Quality of Life, represented by the EQ-5D health utility score will be summarised at each time point and compared between randomised groups using two-sample t-tests. The Quality-Adjusted Life Years (QALYs) accrued over 12 months will be estimated by the area under the health utility curve. The mean QALY difference between groups will be estimated using the method of recycled predictions from an appropriated generalised linear regression model with bootstrapping.

The following cost-related variables will be summarised and compared between groups, using bootstrap estimates of mean differences:

- number of guiding catheters, ordinary guidewires and pressure wires;
- number of adenosine doses;
- number of balloon catheters;
- number of drug eluting stents and bare metal stents;
- use of (and type of) GP IIb/IIIa inhibitor;
- use of bivalirudin;
- use of IVUS and OCT;
- use of intra-aortic balloon pump;
- total radiation dose and contrast use;
- total procedure time;
- days on CCU, ITU and general ward;
- number of echocardiograms, chest x-rays, invasive CV procedures and use of ventilation.

2.1.17 Safety Analysis

The incidence of intra-procedural, post-procedural and in-hospital complications, as recorded on the eCRF, will be summarised. Patient symptoms, changes in haemodynamics and any adverse effects related to the use of adenosine will also be reported.

In addition, the Clinical Events Committee will adjudicate the occurrence of the following safety outcomes:

1. MI associated with revascularisation procedures (Types 4 and 5) (25),
2. Contrast-induced nephropathy (defined as either a greater than 25% increase of serum creatinine or an absolute increase in serum creatinine of 0.5 mg/dL after a radiographic examination using a contrast agent);
3. Bleeding (defined according to the ACUITY criteria: major bleed = intracranial or intraocular bleeding; bleeding at the site of angiography requiring intervention; a haematoma of 5 cm in diameter; a reduction in haemoglobin level of at least 4 g/dL in the absence of overt bleeding or 3 g/dL with a source of bleeding; or transfusion. Non-major bleeding by ACUITY criteria will not be recorded as SAEs (and so would not be reportable to the sponsor) but would be recorded in the eCRF.

These will be summarised and listed.

2.1.18 Follow-up and Timetable

A quality-of-life assessment will be completed at 6-month intervals (EuroQoL, EQ-5D). Clinical follow-up will continue for an average of 1.5 years (range 6-30 months).

Follow-up assessments for adverse events will be performed by the clinical research staff by telephone or in person (eg, outpatient clinic review), as appropriate. Medical records will also be checked. Follow-up contact will occur at 6 monthly intervals until the last patient has achieved a minimum of 6 months of follow-up. Follow-up in the longer term will be

supported by electronic record linkage with central government health records. The active phase of the project is intended to last about 30 months.

2.1.19 Resource use and costs during index hospitalisation

Material use included: catheters, balloons, stents, and drugs. Procedures included: CABG, x-rays, echocardiograms and intravascular ultrasounds. Hospitalization use included: days spent in the Coronary Care Unit (CCU), Intensive Treatment Unit (ITU) and general ward as well as catheterization laboratory time. Events included: severe bleeding, stroke and MI.

The use of a pressure wire in patients randomised to coronary angiography alone was removed from the cost estimates as it was protocol driven. Instead, coronary guidewire use was included.

Equipment costs were derived from National Procurement. Average drug dosages were estimated using NICE guidance (www.evidence.nhs.uk) while unit costs were derived from the British National Formulary (www.bnf.org). Procedure unit costs (except CABG) as well as CCU and ITU unit costs were derived from the Golden Jubilee National Hospital. Catheterization laboratory time (per hour) was derived from Information Services Division Scotland. To estimate the general ward day cost, inpatient excess bed day costs were taken from the NHS Reference Costs for acute or suspected myocardial infarction (Healthcare Resource Group [HRG] code EB10Z). The procedure cost of CABG (HRG EA14Z) was derived from the NHS Reference Costs. Event costs were derived from NHS Reference Costs. The HRG code used for stroke was AA22A and AA22B; for myocardial infarction, EB10Z. No patients experienced a severe bleed and thus it was not included. All costs were presented in 2014 pound sterling.

To incorporate uncertainty, trial results were bootstrapped with stratification by randomization group. We used 10,000 resamples. Where costs were uncertain, they were randomly sampled from gamma distributions using Monte Carlo simulation methods. Confidence intervals were reported as the 2.5th and 97.5th percentiles of the bootstrapped results. Two-sided p-values were calculated on the bootstrapped replicates. They represent the probability of getting something more extreme than what was observed. This is calculated as the proportion of replicates less than and greater than the observed mean cost difference:

$$p = \frac{\text{sum}(X < \bar{X} - \bar{\delta}) + \text{sum}(X > \bar{X} + \bar{\delta})}{\# \text{ replicates}},$$

X is a vector of bootstrapped mean cost differences, \bar{X} is the mean cost difference and $\bar{\delta}$ is the extreme value which is the absolute value of \bar{X} . This method is analogous to a one-sample t-test on the bootstrap replicates of mean cost differences where $\bar{\delta}$ is tested on the distribution X .

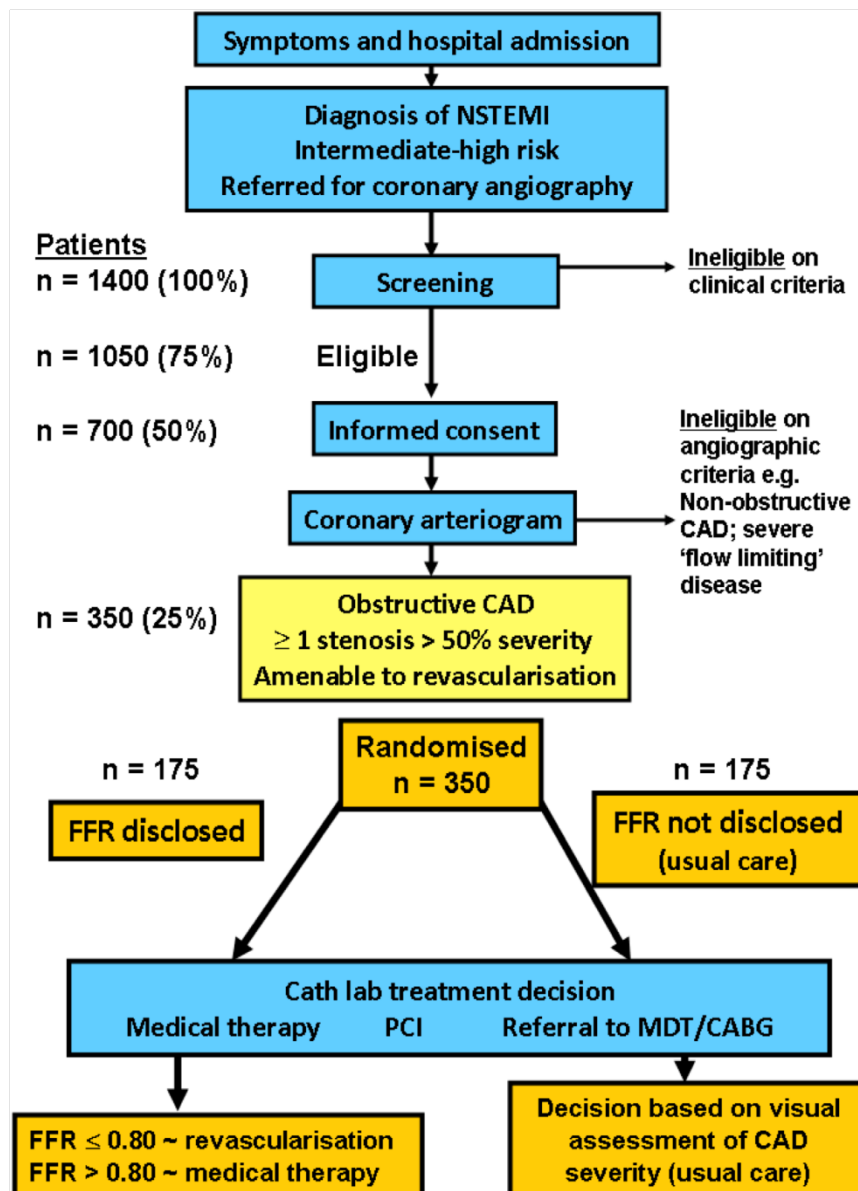


Figure 10: Flow Diagram of FAMOUS NSTEMI Study

2.2 MRI Study

As part of the FAMOUS-NSTEMI trial, we performed an MRI substudy in selected patients. The cardiac MRI scanner was located at the British Heart Foundation cardiovascular research centre at the university of Glasgow. This was at a remote location in relation to the main study site (Golden Jubilee National Hospital). Patients who were admitted to the Golden Jubilee National hospital and Hairmyres hospital were eligible for the study. Patients eligible for the study had to provide their own transport to the research centre. During the CMR examination, a study doctor, a physicist and a radiographer supervised all scans.

The purpose of the CMR substudy was to compare FFR measured invasively with adenosine stress perfusion CMR. We also wanted to compare traditional edema imaging methods with more contemporary parametric mapping sequences in NSTEMI.

2.2.1 Informed consent

Obtaining written consent for MRI

Patients were approached by a member of the healthcare team (myself or research nurse) during the course of routine healthcare provision. Participants were invited to have an MRI scan in the MRI Facility in the BHF Glasgow Cardiovascular Research Centre. For the CMR to take place, at least two members of staff who were trained and experienced in MRI were present. Following informed consent, a standard MRI checklist was completed. The purpose of this checklist was to ensure that the subject did not have any contraindications to MRI, such as a metal foreign body (e.g. replacement heart valve or metal implant), and that the scan was safe to perform. The subject was provided with headphones both in order to hear

the MRI scanner operator (who was in the neighbouring control room) and also to listen to music if desired.

Where possible serial adenosine stress perfusion cardiac MRI at 3 Tesla were be performed on 3 occasions:

- 1) Before angiography: early after acute MI (≤ 7 days after hospital admission) to determine the initial extent of injury,
- 2) After coronary angiography/PCI: 7 – 10 days after admission to assess the outcome of revascularisation (if performed), including new procedure-related MI and determine the early evolution of myocardial pathology (MVO, haemorrhage and oedema)
- 3) Longer-term follow-up: MRI 6 months post-MI to determine final LV outcomes (function and remodelling).

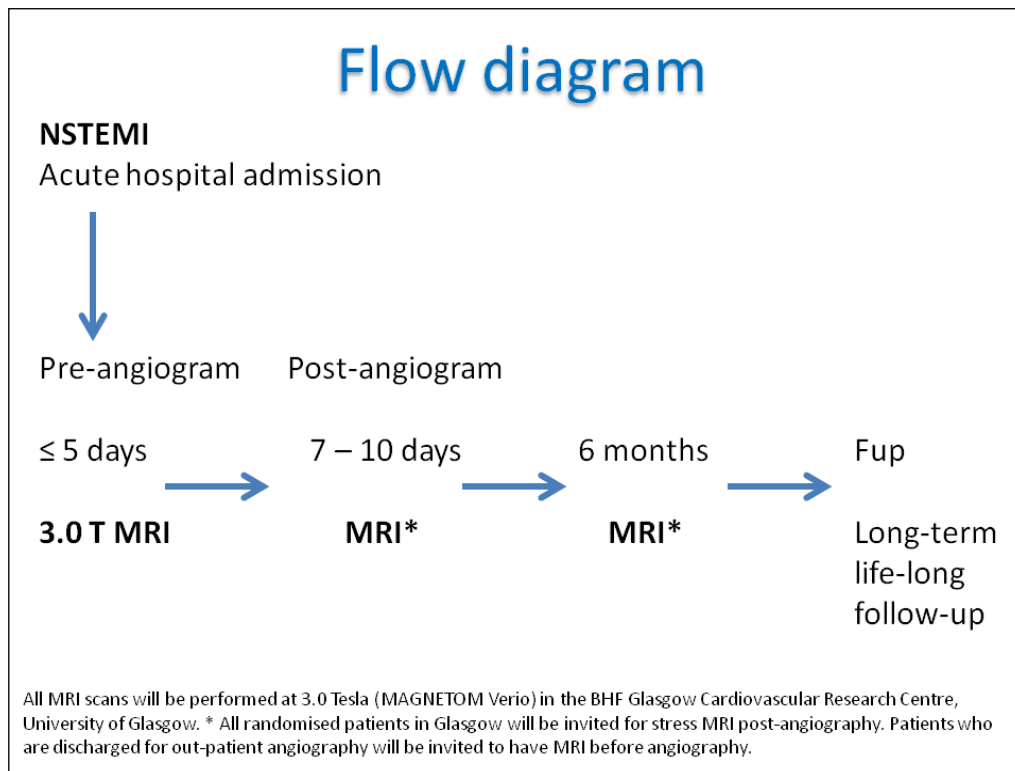


Figure 11: Flow diagram of the FAMOUS - NSTEMI 3.0 Tesla MRI sub-study

2.2.2 CMR protocol

CMR was performed on a Siemens MAGNETOM Verio (Erlangen, Germany) 3.0 Tesla scanner with a 8-element phased array cardiac surface coil. The CMR protocol included localisers then:

- 1) cine MRI with steady state free precession, LV short axis stack, 2 chamber, 4 chamber and 3 chamber views
- 2) T2 maps, T1 maps, T2* maps (short axis slice at base, mid, apex and 4 chamber)
 - WIP 561B – MOLLI *Siemens Healthcare*
- 3) dark blood STIR (short axis slice of base, mid, apex and 4 chamber)
- 4) first pass gadolinium during rest and adenosine stress (short axis base, mid, apex and 4 chamber)
 - WIP 713 perfusion improvements *Siemens Healthcare*

5) 2, 3, 4 and 5 minute short axis stack for early gadolinium enhancement

6) 15-20min for late gadolinium enhancement (short axis stack, 2chamber, 4chamber, 3chamber)

A bolus of gadolinium contrast (Gadovist, Bayer) was administered at 0.1 mmol/kg using a dual-bolus I.V. contrast injection technique.

2.2.2.1 CMR imaging parameters

Cardiac mass and function were assessed using retro-gated (trueFISP) cine breath-hold sequences. The in-plane resolution was ~2 mm (26 μ l/voxel) and the temporal resolution was ~40 ms within the cardiac cycle. The heart was imaged in multiple parallel short-axis (SAX) planes 7-mm thick separated by 3-mm gaps, as well as in the 2-, 3-, and 4-chamber long-axis views.

First-pass adenosine (140 μ g/kg/min) -stress perfusion MRI was performed with a fast low-angle shot (FLASH) sequence. Segmented phase-sensitive inversion recovery (PSIR) Turbo-FLASH were used for late gadolinium enhancement.

2.2.2.2 CMR image analyses

The CMR scans were anonymised and analysed in random order on a Siemens workstation by a team of staff, including four cardiologists (J.L., C.B., S.W., N.T.), two MRI radiographers (K.L., T.S.), one MRI physicist (C.M.) and one image analyst (S.R.). The team has considerable MRI experience in patients with acute MI, including protocols with bright blood T₂-weighted MRI. Total LV and late contrast enhanced infarct mass were calculated by multiplying volumes by myocardial density (1.05 g/cm³).

Reference ranges used in the laboratory were 105-215g for male left ventricular mass, left ventricular mass for women 70 – 170 g, left ventricular end-diastolic volume for men 77 – 195 ml, left ventricular end-diastolic volume for women 52 – 141 ml, left ventricular end-systolic volume for men 19 – 72 ml and left ventricular end-systolic volume for women 13 – 51 ml.

MRI data was stored on PACS and on secure University databases.

2.2.2.3 Ventricular mass and function

Left ventricular dimensions and volumes and ejection fraction were analysed using computer-assisted planimetry.

2.2.2.4 T1, T2 and T2* Measurements and Area-at-Risk

Quantitative T1, T2 and T2* assessments were independently analysed by two cardiologists. Discordance between observers was resolved by a third cardiologist.

2.2.2.5 T2, T1 and Dark Blood STIR Measurements and Area-at-Risk

A threshold of x2 SD difference in mean signal intensity was adopted to delineate an affected area for both T1 and T2 maps and dark blood imaging(57). The jeopardized area-at-risk on each short axis image was defined as the percentage of left ventricular area delineated by the hyperintense zone on T₂-weighted images(57).

2.2.2.6 Infarct definition and size

Acute infarction and assignment of culprit artery territory: The presence of acute infarction was established with MRI based on abnormalities in cine wall motion, rest first-pass myocardial perfusion, and delayed-enhancement imaging. In addition, supporting changes on the ECG and coronary angiogram were also required. Acute infarction was

considered present only if late gadolinium enhancement (LGE) was confirmed on both the short and long axis acquisitions. The myocardial mass of LGE (grams) was quantified by asemi-automatic detection method using a signal intensity threshold of >5 SD above a remote reference region. Infarct regions with evidence of microvascular obstruction were included within the infarct area. Microvascular obstruction was classified as relevant (central dark zone with a sub-endocardial or intra-mural distribution) and non-relevant (dots or nil) and also expressed as a percentage of total left ventricular mass.

2.2.2.7 Myocardial salvage and Microvascular obstruction

Myocardial salvage was calculated by subtraction of percent infarct size from percent area-at-risk. The myocardial salvage index was calculated by dividing the initial myocardial salvage area by the initial area-at-risk. MVO was defined as a dark zone present on MRI 2, 3, 4 and 5 mins post-contrast injection and also present within an area of late gadolinium enhancement.

2.2.2.8 Perfusion

Regional myocardial perfusion was evaluated dynamically during rest and adenosine stress perfusion MRI. We correlated quantitative parametric findings from stress perfusion MRI with invasive 'gold standard' measurements of regional lesion level ischaemia (FFR).

We implemented the latest methods to optimise sequence performance and image acquisition (CV improvement_713, Siemens Healthcare). The main developments with this new package include:

- accelerated MR imaging with T-PAT / enhanced parallel imaging reconstruction
- improved crusher gradients for noise reduction from stimulated echoes
- phase corrections

- motion correction
- real time cine protocol
- proton density map for surface coil correction for dynamic imaging
- arterial input function TurboFLASH

2.2.2.9 Stress/rest perfusion data processing

Baseline stress and rest perfusion MRI images were analysed side-by-side using dedicated software (Argus Dynamic Signal, Siemens, Erlangen, Germany). The stress and rest perfusion scans were viewed simultaneously, and areas of hypoperfusion were assigned to coronary territories using the American Heart Association coronary arterial 16-segment model (224, 225). In each patient, the coronary artery territories with abnormal perfusion were recorded. In cases of disagreement between observers, a third blinded observer adjudicated.

A perfusion defect was classified as significant according to the presence of ischaemia in 2 segments of a 32 segment model (16-segment AHA model divided into sub-endocardial and sub-epicardial layers) i.e.: > 60 degrees in either the basal or the midventricular slices or > 90 degrees in the apical slice or any transmural defect or two adjacent slices(225).

2.2.3 MRI endpoints

Image analyses was standardised according to left ventricular segmentation based on the AHA model.

Definition of remote zone: The remote zone was defined as an area of myocardium in a non-neighbouring territory, typically 180° from the affected region on an axial scan as appropriate. For serial comparisons, the same territory was evaluated based on anatomical landmarks (e.g. papillary muscles) and position in the long axis of the heart (e.g. % LV length from mitral valve annulus).

2.3 Sample size and duration of follow-up

We hypothesised that at least 100 NSTEMI patients would be enrolled within 2 years. This sample size is sufficiently large to provide robust surrogate MRI information at 6 months. We anticipated that recruitment would be achieved within 2 years and data analyses and statistics would be completed by 2.5 years (end of study).

2.3.1 Statistical analyses

Statistical analyses were carried out using IBM SPSS Statistics software, version 21.0 (Armonk, USA). Normality was tested with the Shapiro-Wilk test. All results are given in a format of mean \pm SD, unless otherwise mentioned.

2.3.2 Area at Risk Sub-Study

Correlations between AAR quantified with T1/T2maps and T2W STIR and APPROACH lesion scores were tested by Pearson or Spearman's methods as appropriate. The level of agreement between AAR quantified with T1/T2 maps and T2W STIR was assessed using Bland-Altman plots and 95% limits of agreement. The 95% limits of agreement were calculated using the mean difference between AAR quantified by the two imaging modalities \pm 2 SD of these differences, and contained approximately 95% of all such

differences. The McNemar exact test was used to compare diagnostic accuracy of T1 and T2 maps and T2W STIR imaging in identifying the infarct-related artery, when compared to current gold-standard method of clinical history, ECG and coronary angiography. An inter-observer agreement reliability analysis, using the Kappa statistic (κ), was performed to determine consistency of infarct-related artery diagnosis among observers. $p < 0.05$ was considered statistically significant.

2.3.3 FFR Vs MRI substudy

Receiver-operator characteristic (ROC) analysis was used to determine the optimal cut-off value for FFR to predict a perfusion defect on MRI. The area under the ROC curve (AUC) was used as a measure of test accuracy.

2.3.3.1 Sample Size Calculation for FFR vs. MRI

We estimated approximately 40% of study participants would have an FFR value ≤ 0.80 at the index coronary angiogram and approximately 20% of the participants would have significant residual obstructive coronary disease after the PCI and the prevalence of perfusion defects overall by stress perfusion MRI will be 30%. Theoretically, there should be close to a 1:1 correspondence agreement with an inducible perfusion abnormality on stress MRI and an FFR ≤ 0.80 . Assuming a true underlying agreement rate of 90% and only one artery studied per patient, a sample size of 104 patients would have approximately 85% power to exclude an agreement rate below 80% based on a one sided 95% confidence interval. In reality more than one artery was studied in many patients, hence increasing the power further.

Chapter 4: The Clinical Utility of Fractional Flow Reserve in Patients with NSTEMI

.Summary

Aim: We assessed the management and outcomes of non-ST segment elevation myocardial infarction (NSTEMI) patients randomly assigned to fractional flow reserve (FFR)-guided management or angiography-guided standard care.

Methods and Results: We conducted a prospective, multicentre, parallel group, 1:1 randomized, controlled trial in 350 NSTEMI patients with ≥ 1 coronary stenosis $\geq 30\%$ of the lumen diameter assessed visually (threshold for FFR measurement) (NCT01764334). Enrolment took place in 6 UK hospitals from October 2011 – May 2013. FFR was disclosed to the operator in the FFR guided-group (n=176). FFR was measured but not disclosed in the angiography-guided group (n=174). FFR ≤ 0.80 was an indication for revascularisation by percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). The median (IQR) time from the index episode of myocardial ischaemia to angiography was 3 (2, 5) days. For the primary outcome, the proportion of patients treated initially by medical therapy was higher in the FFR-guided group than in the angiography-guided group (40 (22.7%) vs. 23 (13.2%), difference 9.5% (95% CI 1.4%, 17.7%), $p=0.022$). FFR disclosure resulted in a change in treatment between medical therapy, PCI or CABG in 38 (21.6%) patients. At 12 months, revascularisation remained lower in the FFR-guided group (79.0% vs. 86.8%, difference 7.8% (-0.2%, 15.8%), $p=0.054$). There were no statistically significant differences in health outcomes and quality of life between the groups.

Conclusion: In NSTEMI patients, angiography-guided management was associated with higher rates of coronary revascularisation compared with FFR-guided management. A larger trial is necessary to assess health outcomes and cost effectiveness.

3.1 Introduction

Non-ST segment elevation myocardial infarction (NSTEMI) is the commonest form of acute coronary syndrome (ACS), the most common indication for invasive coronary angiography, and a leading global cause of premature morbidity and mortality(23).Coronary angiography in ACS patients can detect obstructive coronary artery disease and identify patients who may benefit from coronary revascularisation(23, 89). Usual care is based on visual interpretation of coronary disease severity and management decisions include medical therapy, percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). Visual assessment of lesion severity with coronary angiography may be inaccurate resulting in over- or underestimation of the physiological significance of the lesion (84, 226). Hence judgements made by cardiologists in every day practice are subjective, potentially leading to misdiagnosis and incorrect treatment decisions(227).

An alternative approach involves measurement of the myocardial fractional flow reserve (FFR) using a pressure-sensitive coronary guidewire. FFR assesses the physiological significance of a coronary stenosis and is expressed as the ratio of maximal blood flow in a stenotic artery to maximal flow in an unobstructed artery(116). Recent studies (DEFER (228), FAME (119), FAME-2 (229), and RIPCORDER (230)) have evaluated the value of FFR to guide treatment decisions. An $FFR \leq 0.80$ is an evidence-based physiological threshold that correlates with the presence of inducible ischaemia on non-invasive testing (116). FFR values >0.80 indicate that patients can be managed safely with medical therapy without the need for coronary revascularisation.

FFR measurements require maximal coronary hyperaemia which may be less readily achieved in patients with acute coronary disease because of coronary microvascular dysfunction (127). Recent clinical studies indicate that FFR in this setting may be valid (126,

129)but in the absence of evidence from randomised prospective trials, a routine physiological approach for the management of patients with recent MI is not recommended in guidelines (23).We hypothesised that management decisions in patients with NSTEMI undergoing coronary angiography guided by routine FFR measurement would be feasible and safe, and would provide additive clinical utility compared to standard care based on visual interpretation of the angiogram.

3.2 Methods

Trial design

We performed a prospective 1:1 randomised controlled parallel group trial in 350 NSTEMI patients enrolled from October 2011 to May 2013.

Participants and eligibility criteria and Setting

The inclusion and exclusion criteria as well as the setting are documented in the methods section of this thesis.

Coronary angiogram acquisition and analyses

Coronary angiograms were acquired during usual care with standard cardiac catheter laboratory equipment. The angiograms were assessed visually by the attending clinicians who made the treatment decision for medical therapy, PCI or CABG.

Randomisation, implementation and blinding

Participants were enrolled by research staff on the ward before the angiogram was obtained. The standard care management strategy was established and recorded before FFR was measured. The treatment plan was based on all of the clinical information including the results of the angiogram and before FFR was measured. If the angiographic eligibility criteria were fulfilled, the patients were then randomised by the research nurse in the catheter laboratory to FFR-guided and angiography- guided strategies using a web-based

randomisation system. The randomisation sequence was created using randomised permuted blocks of length 4, without stratification. The allocation sequence was on a 1:1 basis between the FFR-guided group and the angiography-guided group and the sequence was concealed electronically. The participants were blinded to the treatment group allocation.

3.2.1 Interventions

The randomised participants had FFR measured in all coronary arteries with a lesion of $\geq 30\%$ diameter stenosis that were amenable to instrumentation with a pressure-sensitive coronary guidewire (St Jude Medical, Uppsala). FFR was measured during coronary hyperaemia induced by intravenous adenosine (140 $\mu\text{g/kg/min}$). The FFR intervention in this study, including assessment of adenosine effect, measurement of FFR, vessel selection, blinding and disclosure of the FFR results, has been previously described(231).

FFR-guided group: $\text{FFR} \leq 0.80$ was an indication for revascularisation by percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG), as appropriate, and $\text{FFR} > 0.80$ was an indication for medical therapy only. Any changes in management strategy following FFR disclosure were prospectively recorded.

Angiography-guided group and blinding: In patients randomised to the angiography-guided group, FFR was measured in the same way as in the FFR-guided group except that the FFR results were not disclosed. The research staff obscured the haemodynamic monitor (RadiAnalyzer Xpress (St Jude Medical, Uppsala)) from the clinicians, nurses and patients such that it was impossible for them to observe the pressure wire information either in the catheter laboratory or afterwards. Electronic displays of distal coronary pressure on other haemodynamic monitors that may have been visible in the catheter laboratory were also disabled. Quality control checks, including assessments of equalised pressure recordings and verification of symptoms and haemodynamic changes with intravenous adenosine, were

conducted in the usual way. The quality assurance procedures have been previously described (231).

3.2.2 Outcomes

Primary outcome

The pre-specified primary outcome was the between-group difference in the proportion of patients allocated to medical management. The final treatment decision was made by the clinicians in the cardiac catheter laboratory during the index procedure or shortly afterwards if a multidisciplinary heart team review was indicated.

Secondary outcomes

- 1) The feasibility and safety of routine FFR measurement.
- 2) The relationship between FFR and coronary stenosis severity by visual assessment of the angiogram.
- 3) Major adverse cardiac events (MACE) during follow-up over 12 months, defined as cardiac death or hospitalisation for myocardial infarction or heart failure after randomisation. Cardiovascular death, stroke, transient ischaemic attack, contrast nephropathy and bleeding were also prospectively recorded. All of these events were adjudicated by a Clinical Event Committee (CEC) comprised of 3 cardiologists who were independent of the trial and blinded to the treatment allocations. Coronary revascularisation, including PCI and CABG, were prospectively recorded in the clinical report form. Information on serious adverse events during follow-up was obtained by contacting the patients by telephone and reviewing their primary and secondary care records. All complications that were potentially related to the invasive procedure were prospectively recorded.
- 4) Index hospitalisation resource use including: material, procedure, hospitalisation and in-hospital event costs.

5) Health-related quality of life (HRQoL; EuroQol 5-Dimensions 3-Level (EQ-5D-3L).

Healthcare resources and costs

Costs during index hospitalisation were calculated by applying resource use or events at the individual level to unit costs derived from NHS National Procurement, NHS Reference Costs, Information Services Division Scotland, the British National Formulary (www.bnf.org) and the Golden Jubilee National Hospital.

Sample size

We calculated that 322 randomised subjects (161 subjects in each group) would provide 90% power at a 5% level of significance to detect a 50% relative increase in the proportion of patients assigned to medical treatment in the FFR disclosed group from 15% to 30%. This difference was based on observations made in a pilot study(82) intended to inform the design of the current trial. Allowing for loss of data at the time of the procedure the number of participants in the randomised trial was increased to 350.

3.4 Statistical methods

Mean (standard deviation) or median (inter-quartile range) were used to summarise continuous data. Counts and percentages were used to summarise categorical data. All tests were two-tailed and assessed at the 5% significance level.

The primary outcome of the proportion of patients allocated to medical therapy was assessed in terms of the difference in proportions and the relative risk between groups estimated with exact 95% confidence intervals and p values. The proportion of patients with major adverse cardiovascular events (MACE) within 12 months and other binary outcomes were analysed using the same methods, and time to events within 12 months was compared

between groups using log rank tests. Health related quality of life was compared between groups using baseline-adjusted linear regression. Length of stay was compared between groups using a Wilcoxon Rank Sum test. Costs were compared using bootstrapping (details in Supplementary Methods). The statistical analyses were performed using R version 3.0.0 and StatXact version 5.0.3.

3.5 Results

Eight hundred and fifty three NSTEMI patients were referred for invasive management and gave informed consent from October 2011 to May 2013 (Figure 12). Of these, 350 patients (mean age 62 years, 74% male) were randomised (n=176 FFR-guided, n=174 angiography-guided).

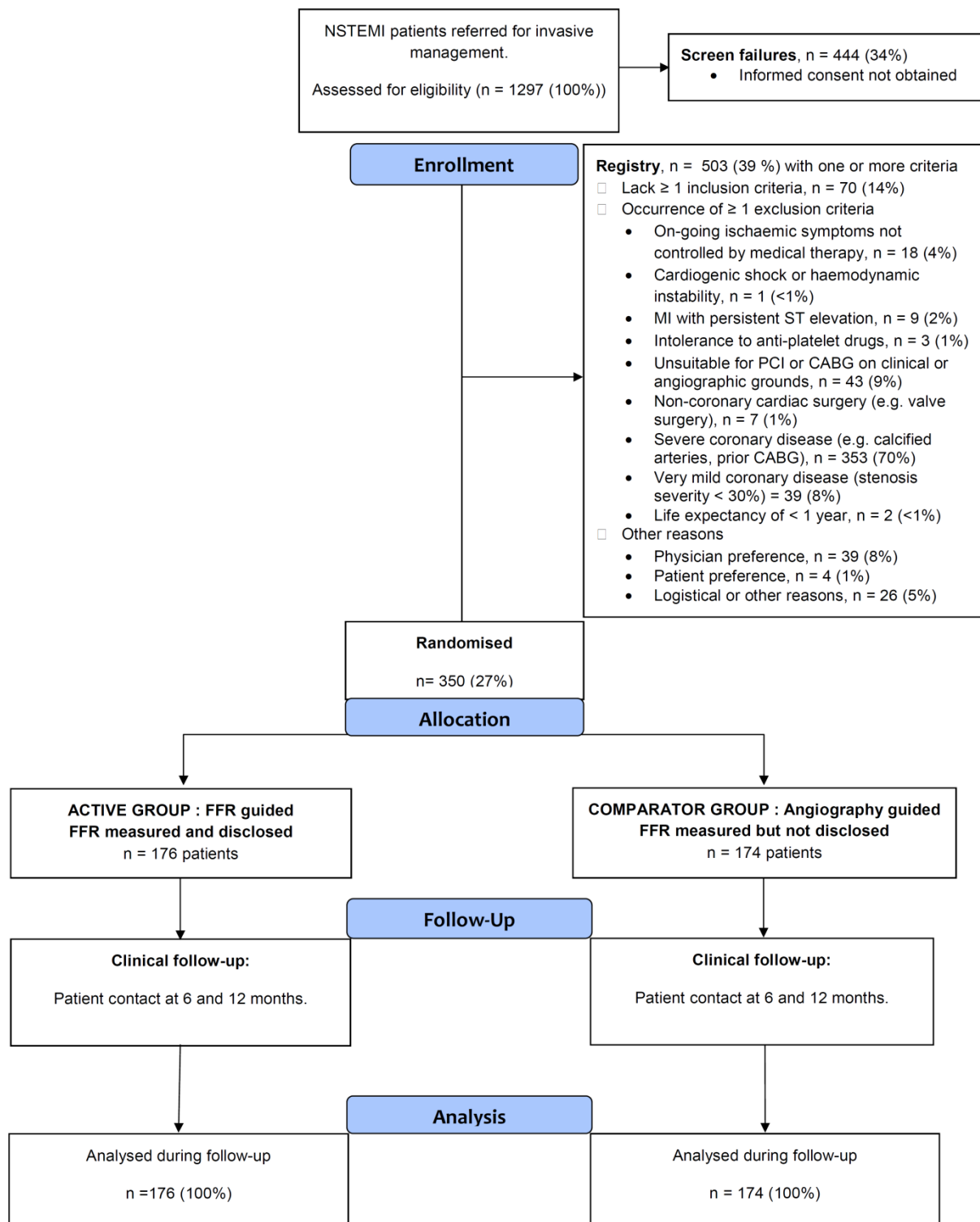


Figure 12: Flow diagram of the clinical trial.

FFR was measured in all (100%) participants but only disclosed in the FFR-guided group. The clinical and treatment characteristics of the patients included in the FFR-guided group and the angiography-guided group were similar (Table 3).

322 (92%) of 350 randomised participants had a history of angina at rest (Canadian Cardiovascular Society Angina Class IV angina) and 280 (80%) patients had ECG evidence of ischaemia. The median (interquartile range) time from the index episode of myocardial ischaemia to the invasive angiogram was 3 (2, 5) days and 81% of the participants underwent angiography within 5 days of the index event or most recent episode of chest pain. Further detail on the relationship between time from index event to procedure and its impact on FFR are provided in table 2. All patients were followed up for 12 months and all of the randomised participants were included in the analysis.

Table 2: Relationship between Time of Index Event and FFR

		Time from index event to procedure		p
		>3 days	≤3 days	
		n; mean FFR (SD)	n; mean FFR (SD)	
FFR	Segments	336; 0.71 (0.18)	368; 0.68 (0.18)	0.063
	Vessel Groups	326; 0.70 (0.18)	358; 0.68 (0.18)	0.095
	Arteries	306; 0.70 (0.19)	338; 0.67 (0.18)	0.065
	Patients	166; 0.62 (0.18)	184; 0.57 (0.15)	0.008

Table 3: Baseline clinical and angiographic characteristics of all-comers.

Baseline characteristics*		Randomly assigned groups	
		FFR-guided	Angiography-guided
		group	group
		n = 176	n = 174
<i>Clinical</i>			
Age, years		62.3 (11.0)	61.6 (11.1)
Male sex, n (%)		133 (75.6%)	127 (73.0%)
Heart rate, bpm		73 (15)	74 (17)
ECG evidence of ischaemia at initial presentation, n (%)		137 (77.8%)	143 (82.2%)
Peak troponin concentration before the procedure*			
> x5 upper limit of normal		129 (73.3)	137 (78.7)
> x10 upper limit of normal		107 (60.8)	115 (66.1)
GRACE score for death or myocardial infarction within 6 months of admission		146 (131, 173)	146 (122, 172)
Patients with a GRACE score for death or myocardial infarction within 6 months > 140, n (%)		102 (58.0%)	97 (55.7%)
Diabetes mellitus‡, n (%)		26 (14.8%)	26 (14.9%)
History of atrial fibrillation or flutter, n (%)		12 (6.8%)	7 (4.0%)
History of stroke or transient ischaemic attack‡, n (%)		15 (8.5%)	9 (5.2%)
History of peripheral vascular disease‡, n (%)		14 (8.0%)	14 (8.0%)
Previous myocardial infarction, n (%)		22 (12.5%)	24 (13.8%)
Previous percutaneous coronary intervention, n (%)		19 (10.8%)	19 (10.9%)
History of treated hypertension‡, n (%)		78 (44.3%)	81 (46.6%)
History of treated hypercholesterolaemia‡, n (%)		71 (40.3%)	56 (32.2%)
History of smoking‡, n (%)			
Current		72 (40.9%)	71 (40.8%)
Former (stopped > 3 months)		55 (31.2%)	47 (27.0%)
Never		49 (27.8%)	56 (32.2%)
Angina, Canadian Cardiovascular Society angina class at presentation, n (%)	I	1 (0.6%)	0 (0%)
	II	1 (0.6%)	2 (1.1%)
	III	7 (4.0%)	15 (8.6%)
	IV	166 (94.3%)	156 (89.7%)
New York Heart Association functional class at presentation, n (%)	I	154 (87.5%)	154 (88.5%)
	II	17 (9.7%)	16 (9.2%)
	III	2 (1.1%)	3 (1.7%)
	IV	3 (1.7%)	1 (0.6%)
Frailty, n (%)*	Well	148 (87.1%)	144 (87.8%)
	Vulnerable	20 (11.8%)	17 (10.4%)
	Frail	2 (1.2%)	3 (1.8%)
Health-related quality of life, EQ-5D score		0.78 (0.29)	0.81 (0.25)
<i>Medication at procedure</i>			
Aspirin, n (%)		175 (99.4%)	173 (99.4%)
P2Y12 inhibitor, n (%)		176 (100%)	173 (99.4%)
Statin, n (%)		168 (95.5%)	167 (96.0%)
Beta-blocker, n (%)		161 (91.5%)	147 (84.5%)
Calcium channel blocker, n (%)		27 (15.4%)	25 (14.4%)
Isosorbide mononitrate, n (%)		18 (10.2%)	20 (11.5%)
Intravenous nitrate, n (%)		32 (18.2%)	21 (12.1%)
Low molecular weight heparin, n (%)		165 (93.8%)	168 (96.6%)

Footnote: ECG = electrocardiogram. Means \pm SD or median (interquartile range) for normal and non-normally distributed data, respectively. Categories for peak troponin I and T concentrations were determined based on the upper limit of normal (99th centile) for each hospital; ‡ At least one risk factor for coronary artery disease was required for eligibility. Diabetes mellitus was defined as a history of diet-controlled or treated diabetes. Frailty was assessed using the frailty index score (Supplementary Methods³⁷) and the 6 categories were summarised into 3 groups: Well, Vulnerable, or Frail.

3.5.1 FFR-guided vs. Angiography-guided treatment groups

FFR was measured in 704 (99.7%) of 706 lesions with a stenosis severity $\geq 30\%$, and was measured in at least one artery in all (100%) patients. Of lesions with an FFR result (n=704), 430 (61.1%) were physiologically significant ($\text{FFR} \leq 0.80$) (Table 4 and figure 13)

Table 4: Procedure characteristics and findings.

Characteristics*	Randomly assigned groups	
	FFR-guided group n = 176	Angiography-guided group n = 174
Procedure		
Time from index episode of myocardial ischaemia to the invasive angiogram, days	3 (1, 4)	4 (2, 5)
Procedure characteristics		
Radial artery access, n (%)	158 (89.8%)	157 (90.2%)
Procedure time (including angiography and PCI), min	66.5 (23.4)	70.5 (33.5)
Volume of contrast used, ml	218.7 (97.3)	221.9 (110.4)
Number of stents per patient	1.1 (1.1)	1.4 (1.2)
Total stent length per patient, mm	24.4 (24.7)	29.4 (26.9)
Total number of stents	203	245
Total number of lesions with a stenosis $\geq 30\%$ of the reference diameter of the artery	355	351
Total number of lesions with a stenosis $\geq 50\%$ of the reference diameter of the artery (% of all lesions)	331 (93.2%)	314 (89.5%)
Patients with at least one lesion $\geq 50\%$ severity in the left main artery, n (%)	2 (1.1%)	6 (3.4%)
FFR findings		
Lesions successfully measured for FFR, number / total number (%)	355 (100%)	349 (99.4%)
Number of physiologically significant (FFR ≤ 0.80) lesions (% of all lesions)	208 (58.6%)	222 (63.6%)
Arteries with at least one physiologically significant (FFR ≤ 0.80) lesion, n (%)		
0	34 (19.3%)	29 (16.7%)
1	91 (51.7%)	90 (51.7%)
2	39 (22.2%)	42 (24.1%)
≥ 3	12 (6.8%)	13 (7.5%)
Patients with at least one physiologically significant lesion (FFR ≤ 0.80), n (%)	142 (80.7%)	145 (83.3%)
Patients with at least one physiologically significant lesion (FFR ≤ 0.80) in the proximal or middle left anterior descending artery, n (%)	72 (40.9%)	86 (49.4%)
Mean FFR in lesions with FFR ≤ 0.80	0.56 (0.12)	0.58 (0.13)
Lesion characteristics based on visual interpretation of the angiogram		
Stenosis, n (%)		
30 - 49% of diameter	24 (6.8%)	37 (10.5%)
50 - 69% of diameter	76 (21.4%)	73 (20.8%)
70 - 89% of diameter	113 (31.8%)	88 (25.1%)
$\geq 90\%$ of diameter	111 (31.3%)	124 (35.3%)
Total occlusion	31 (8.7%)	29 (8.3%)

Footnote: TIMI = Thrombolysis in Myocardial Infarction grade. Mean \pm SD or median (interquartile range) for normal and non-normally distributed data, respectively. A diseased artery was defined as an epicardial artery with one or more lesions $\geq 30\%$ of the reference vessel diameter and amenable to PCI or CABG. An angiographically significant artery was defined as an artery with one or more lesions $\geq 50\%$ of the reference vessel diameter.

Ten participants (2.9%) had no lesions (stenosis severity $< 50\%$) when assessed by angiography and 63 (18.0%) patients had no lesions when subsequently assessed by FFR (>0.80). The number of patients with 0, 1, 2, or ≥ 3 vessel coronary disease is shown in Figure 13.

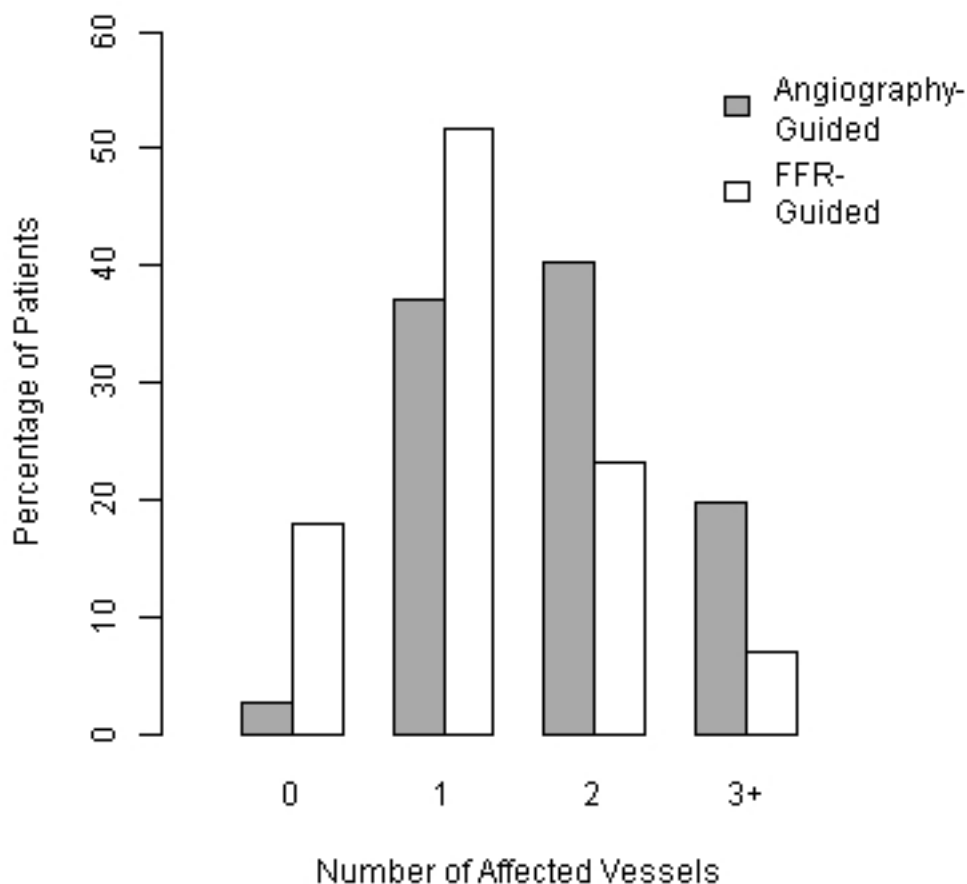


Figure 13: Number of Affected Vessels in Angiographic and FFR Guided Arms

3.5.2 Primary outcome

The proportion of patients treated by medical therapy was higher in the FFR-guided group than in the angiography-guided group (40 (22.7%) vs. 23 (13.2%), difference 9.5% (95% CI 1.4%, 17.7%), $p=0.022$; relative risk 1.72 (1.08, 2.82)) (Table 5).

The initial treatment decisions before randomisation and after FFR disclosure in the FFR-guided group are shown in Figure 14. FFR-disclosure resulted in a change in treatment plan in 38 (21.6%) of 176 patients. The relationship between FFR and stenosis severity is shown in Figure 15 and 16.

Table 5: Outcomes in FFR guided and Angio Guided Groups

	Randomly assigned groups			
Outcome*	FFR- disclosure group n = 176	Angiography group n = 174	Risk Difference (95% CI)	p value†
Primary outcome[‡]				
Medical management, n (%)	40 (22.7%)	23 (13.2%)	9.5% (1.4%, - 17.7%)	0.022
Coronary revascularisation during the index admission	136 (77.3%)	151 (86.8%)		
Percutaneous coronary intervention, n (%)	125 (71.0%)	139 (79.9%)	-8.9% (-18.1%, - 0.2%)	0.057
Coronary artery bypass graft, n (%)	11 (6.2%)	12 (6.9%)	-0.7% (-6.2%, 4.8%)	0.87
In-hospital adverse events				
Contrast nephropathy	2 (1.1%)	1 (0.6%)	0.6% (-2.2%, 3.5%)	0.69
Major Bleeding	2 (1.1%)	1 (0.6%)	0.6% (-2.2%, 3.5%)	0.69
Health outcomes at 12 months				
Cardiovascular death, non-fatal myocardial infarction, unplanned hospitalisation for stroke or transient ischaemic attack (MACCE)	13 (7.4%)	16 (9.2%)	-1.8% (-7.9%, 4.2%)	0.56
Cardiac death, non-fatal myocardial infarction or unplanned hospitalisation for heart failure (MACE)	14 (8.0%)	15 (8.6%)	-0.7% (-6.7%, 5.3%)	0.89
MACE, excluding procedure-related myocardial infarction††	10 (5.7%)	5 (2.9%)	2.8% (-1.6%, 7.6%)	0.25
All-cause death	5 (2.8%)	3 (1.7%)	1.1% (-2.4%, 5.0%)	0.54
Fatal or non-fatal myocardial infarction††	11 (6.2%)	15 (8.6%)	-2.4% (-8.2%, 3.3%)	0.49
Myocardial infarction related to coronary revascularisation (Type 4a, Type 4b and Type 5 myocardial infarction)	5 (2.8%)	11 (6.3%)	-3.5% (-8.5%, 1.1%)	0.12
Spontaneous myocardial infarction	7 (4.0%)	5 (2.9%)	1.1% (-3.1, 5.5%)	0.69
Heart failure	1 (0.6%)	0 (0.0%)	0.6% (-1.6%, 2.8%)	0.51

			3.2%)	
Stroke or TIA	0 (0.0%)	1 (0.6%)	-0.6% (-3.2%, 1.5%)	0.52
Other secondary outcomes			<i>Mean Difference</i>	<i>p value</i>
			<i>(95% CI)</i>	
Health-related quality of life: EQ-5D health status at 12 months	0.844 (0.236)	0.804 (0.284)		
Change from baseline health status at 12 months	0.066 (0.357)	-0.010 (0.276)	0.055 (-0.010, 0.120)	0.095
Cost through index hospitalisation, mean (SE) £	7,289 (608)	7,484 (632)	-194 (-961 to 575)	0.61
Material cost, mean (SE) £**	1,095 (39)	822 (46)	274 (157 to 389)	<0.01
Procedure cost, mean (SE) £**	467 (111)	502 (118)	-35 (-307 to 227)	0.78
Hospitalisation cost, mean (SE) £**	5,701 (585)	6,117 (611)	-415 (-1,069 to 239)	0.21
In-hospital event cost, mean (SE) £**	25 (19)	43 (19)	-18 (-69 to 37)	0.46
Duration of hospital stay at baseline admission, days	6.1 (3.3)	6.5 (3.1)	-0.44 (-9.41 to 8.51)	0.09

Means±SD and median (interquartile range) are used for normal and non-normally distributed data. Cost data are reported as mean±SE† FFR was measured in all participants and disclosed in the FFR-guided group but not disclosed in the angiography-guided group. The P value is the comparison between the FFR-guided group and angiography-guided group. ¢ The index treatment decision as per randomised strategy occurred in 171 (97.2%) of the participants in the FFR guided group and 173 (99.4%) of the participants in the angiography-guided group. ¥ The odds ratio calculations are described in the Methods. †† Of the 10 patients with spontaneous MACE in the FFR group, FFR disclosure changed the initial treatment plan from PCI to medical therapy for the culprit artery in 4 patients. These events happened from 3 - 11 months after randomisation. The excess of 5 patients with a spontaneous MACE in the FFR group is due to 2 deaths, 2 patients with spontaneous MI and 1 patient with a heart failure hospitalisation. †† Myocardial infarction: 28 non fatal MI

events and 2 fatal MI events occurred within 12 months of randomisation in 26 patients, including 17 procedure - related MIs in 16 patients (one standard care patient had two procedure-related MIs (index procedure and a subsequent procedure during follow-up)) and 11 spontaneous MIs in 10 patients (one FFR patient had two of these events)). Twenty six patients had at least one MI event. Four patients had two MI events (n=2 FFR-guided group, n=2 angiography-guided group). In summary, one patient had two procedure-related MIs, one patient had two spontaneous MIs and two patients had both types of MI.

** Material costs includes: guide catheters, ordinary guidewires, pressure wires, adenosine, balloon catheters, drug eluting stents, bare metal stents, GP inhibitors and bivalirudin;

Procedure costs includes: CABG, intravascular ultrasound, optical coherence tomography, echocardiogram and chest x-ray; hospitalisation costs includes: catheterisation laboratory

time, CCU days, ITU days and general ward days; in-hospital events included MI and stroke.

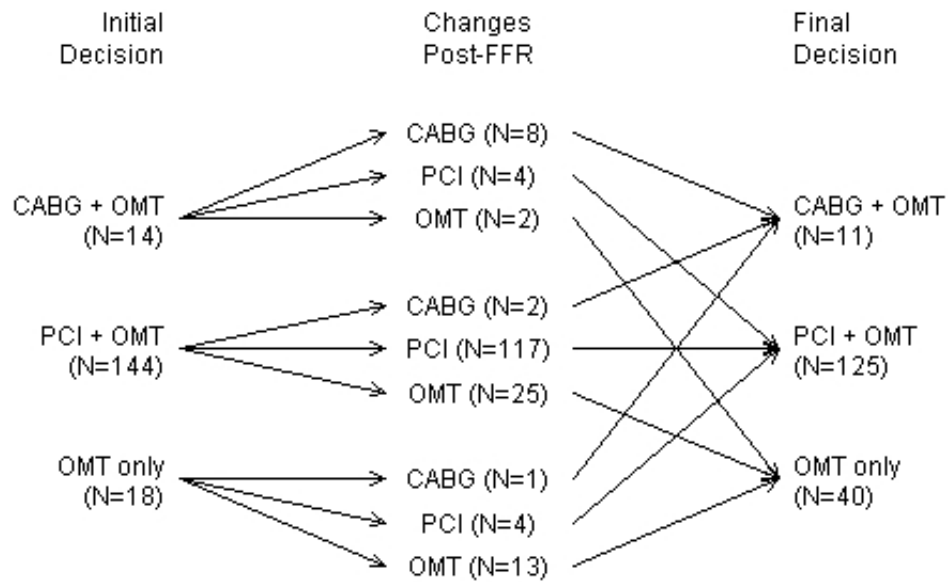


Figure 14: FFR-guided group: treatment decisions initially based on angiography alone and then finally after FFR disclosure.

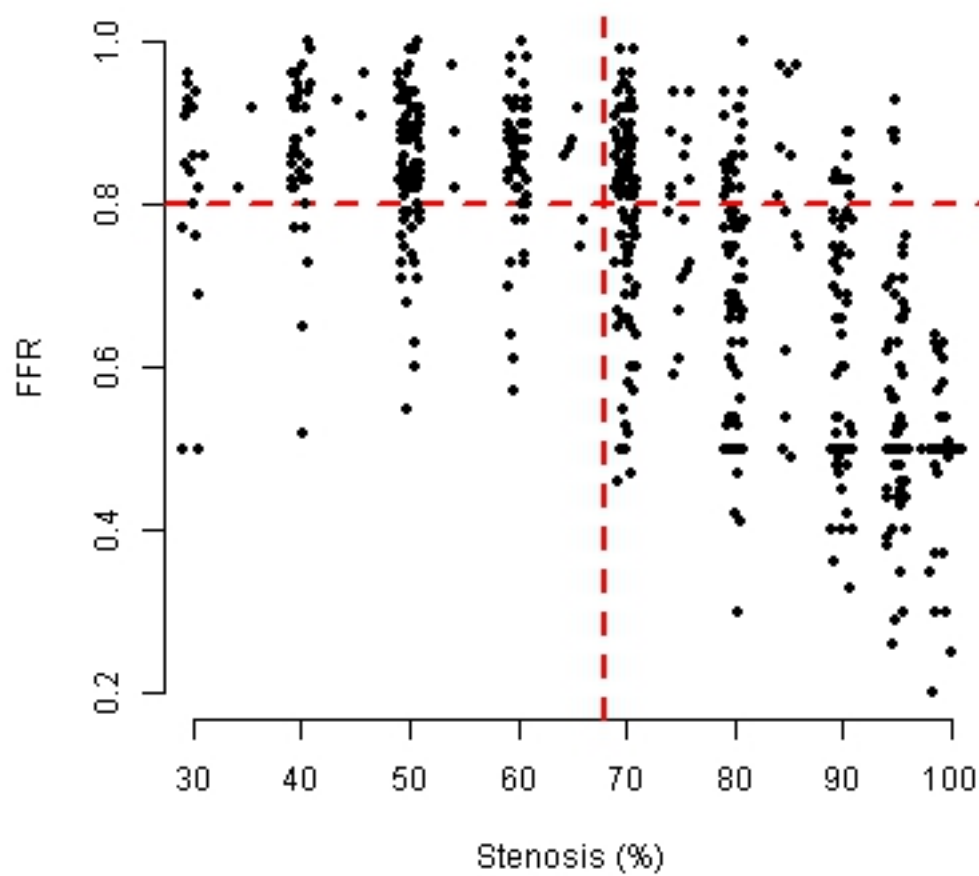


Figure 15: Relationship between angiographic stenosis severity assessed visually before randomisation and FFR (all lesions).

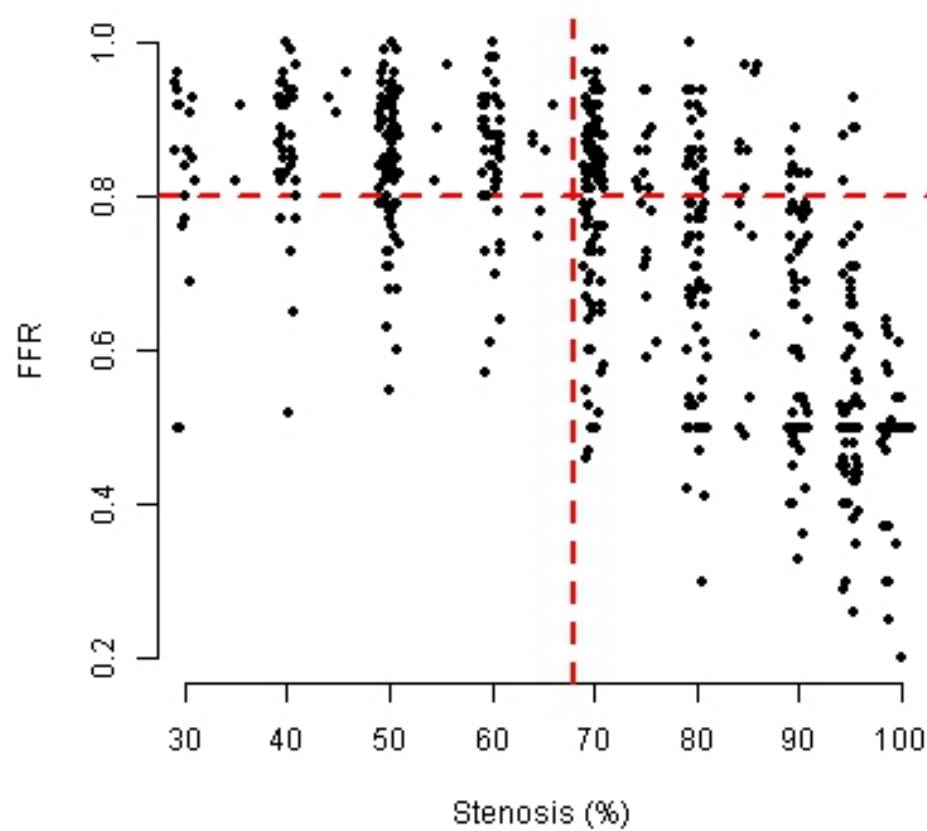


Figure 16a: Relationship between angiographic stenosis severity assessed visually before randomisation and FFR in culprit vessels.

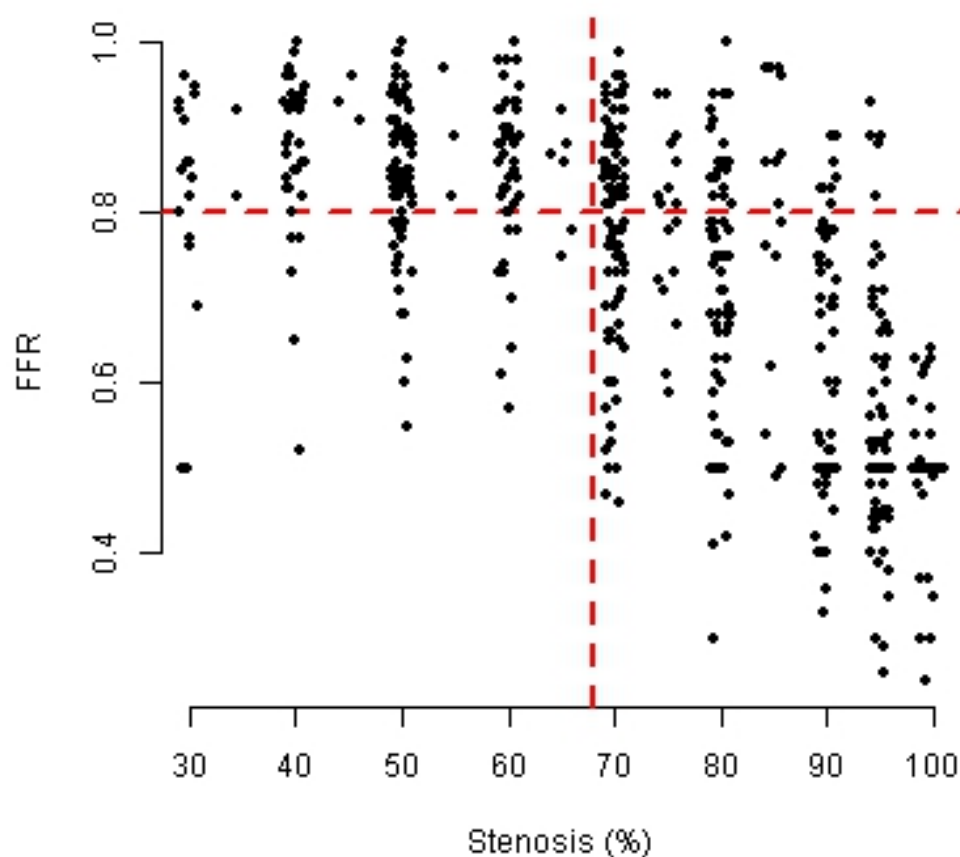


Figure 16b: Relationship between angiographic stenosis severity assessed visually before randomisation and FFR in non-culprit vessels.

3.5.3 Resource use and material costs during the index hospitalisation

The duration of the index invasive procedure, the volume of radiographic contrast medium, and the number, type (drug eluting stent vs. bare metal stent) and length of stents were similar in the FFR-guided group and angiography-guided groups (Table 5). Mean material costs were higher in the FFR-guided group (£1,095, 95% confidence interval £1,021 to £1,171) compared to the angiography-guided group (£822, 95% confidence interval £737 to £914). Mean in-hospital healthcare costs were similar in the FFR-guided group (£7,289,

95% confidence interval £6,173 to £8,549) and the angiography-guided group (£7,484, 95% confidence interval £6,325 to £8,777) (Table 5).

3.5.4 Clinical events and safety

In-hospital adverse events relating to procedure safety are described in Table 5. According to independent adjudication based on review of the coronary angiograms, 8 coronary artery dissections occurred in 7 (2.0%) of 350 patients during the index procedure. Six dissections were attributed to coronary instrumentation during PCI and 2 were attributed to the pressure wire.

The follow-up assessments were completed in June 2014. Vital status at 12 months was obtained for all (100%) participants (Table 5). Fourteen (8.0%) of 176 patients in the FFR-guided group and 15 (8.6%) of 174 in the angiography-guided group experienced cardiac death, non-fatal myocardial infarction or heart failure hospitalisation ($p=0.89$) (Table 3; Figure 17). Myocardial infarction relating to PCI (Type 4a or Type 4b) or CABG (Type 5) occurred in 5 (2.8%) patients in the FFR-guided group and 11 (6.3%) patients in the angiography-guided group ($p=0.12$) (Table 5). MACE excluding MI related to revascularisation occurred in 10 (5.7%) patients in the FFR-guided group and 5 (2.9%) patients in the angiography-guided group ($p=0.25$) (Table 5; Figure 17 and 18). Table 6 shows the clinical vignettes for those patients in the FFR guided arm who had a MACE event.

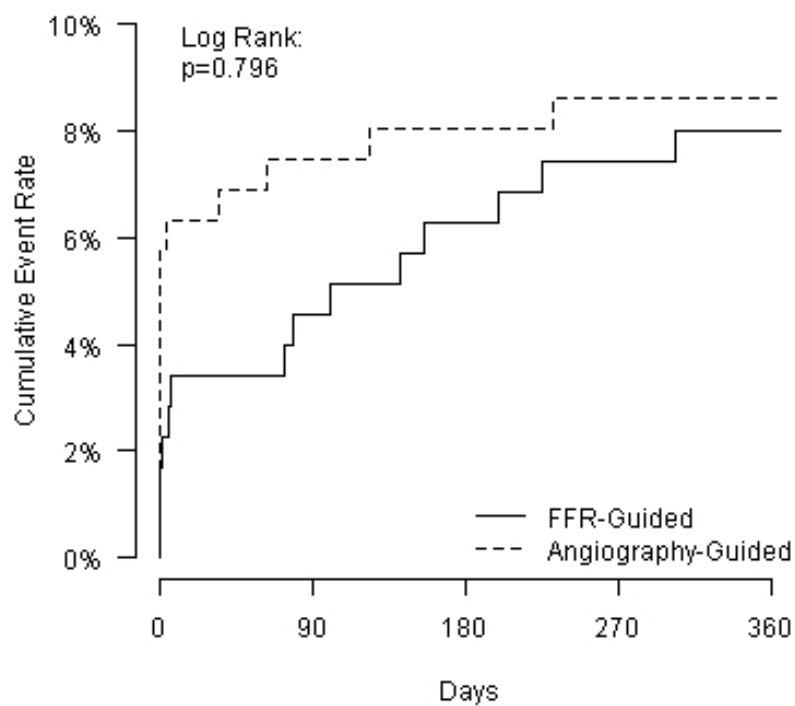


Figure 17: Kaplan-Meier plots for major adverse cardiac events (MACE) during 12 months follow-up in the FFR-guided group and angiography-guided group.

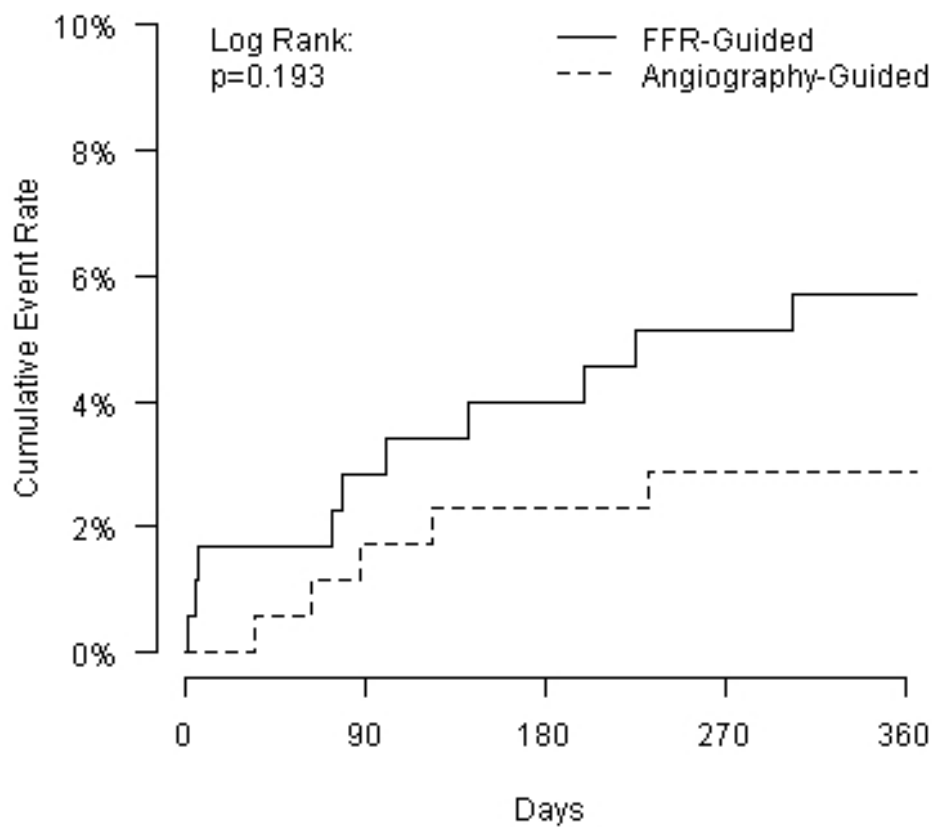


Figure 18: **Kaplan-Meier plots for major adverse cardiac events (MACE) during 12 months follow-up in the FFR-guided group and angiography-guided group. MI events associated with revascularisation (Types IV and V MI) are excluded so the MACE outcome includes spontaneous MI events post-randomisation only.**

Table 6 – Adverse Events in FFR guided Patient

Participant (age, sex)	Invasive findings for culprit lesion (location, angiographic stenosis severity)	Invasive findings for non-culprit lesion (location, angiographic stenosis severity)	Initial treatment plan based on the angiogram	FFR result and treatment plan after FFR disclosure	Adverse cardiovascular event and treatment*
Male	Intermediate artery, 70% focal stenosis, FFR = 0.86	No lesions	PCI	Medical therapy	NSTEMI 7 weeks after randomisation PCI performed to culprit intermediate artery stenosis
Male	Proximal circumflex, 70% stenosis	Mid left anterior descending artery, 60% stenosis	PCI	Circumflex artery FFR = 0.94, Left anterior descending artery FFR = 0.83; Medical therapy	NSTEMI 8 months after randomisation Medical management.
Male	Right coronary artery, 100% stenosis	Mid left anterior descending artery, 60% stenosis	CABG	FFR = 0.87 Medical therapy	Severe left ventricular dysfunction at baseline (LV ejection fraction < 30%) but no implantable defibrillator; sudden cardiac death
Male	Proximal left anterior descending coronary artery, 75% focal stenosis.	No lesions	PCI to culprit lesion	FFR = 0.86 Medical therapy	Coronary guidewire related dissection during the index procedure; FFR- guided decision for medical therapy changed to PCI in order to treat the dissection. PCI was performed but MI did not occur.

3.5.5 Health outcomes in patients treated initially with medical therapy alone

Sixty three (18.0%) of 350 randomised participants were initially managed medically without revascularisation. Of these, 3/40 (7.5%) in the FFR-guided group had a MACE event during 12 months follow-up vs. 0/23 (0%) in the angiography-guided group ($p=0.22$; Table

3.5.6 Revascularisation within 12 months

Compared with the angiography-guided group, the percentage of patients who were free from coronary revascularisation remained higher in the FFR disclosure group at 12 months (37 (21.0%) vs. 23 (13.2%), difference 7.8% (-0.2%, 15.8%), $p=0.054$; relative risk 1.59 (0.99, 2.62)).

3.5.7 Health-related quality of life

Health-related quality of life scores were similar in each group at 12 months (Table 5).

3.6 Discussion

In this trial we assessed a routine physiological approach combined with coronary angiography to diagnose and treat coronary artery disease in patients with recent NSTEMI undergoing invasive management.

Compared with an anatomical approach based on visual interpretation of the coronary angiogram (standard care), FFR-guided management was feasible and safe in the catheter laboratory. The FFR-guided approach resulted in changes in stenosis classification and patient management in one fifth of the patients. The rate of coronary revascularisation was reduced at the index procedure and most of this difference was maintained at 12 months. Material costs during the index procedure increased because of the cost of the pressure wire but overall healthcare costs during the index hospitalisation were similar. MI related to revascularisation tended to be more frequent in the standard care group whereas MACE events unrelated to revascularisation tended to be more common in the FFR group. There was no evidence for differences in the other health outcomes or in health-related quality of life between the randomised groups.

The results of this trial have several implications. Firstly, routine FFR measurement in appropriately selected NSTEMI patients was feasible in all of the participants and relatively safe. Radial artery access was the norm and bleeding complications were rare. Secondly, on an individual patient basis, FFR disclosure commonly changed patient management (Figure 14), and overall, revascularisation was reduced. Thirdly, compared with the angiography guided group, the increased adoption of medical therapy at the expense of revascularisation in the FFR disclosure group was associated with similar overall health outcomes and quality of life at 1 year. Representing a balance of competing risks, the reduction in procedure-related MI events in the FFR group should be considered against the increase in spontaneous cardiac events during follow-up. Finally, based on the combination of coronary angiography and the use of FFR, the diagnostic

work-up of patients admitted with NSTEMI could be simplified ruling out the need for deferred management and non-invasive stress testing in NSTEMI patients with a broad range of stenosis severities ($\geq 30\%$).

In invasively managed NSTEMI patients, the standard care approach involves visual interpretation of the anatomical severity of disease disclosed by the coronary angiogram. Adoption of a physiological approach to inform treatment decisions in invasively managed NSTEMI patients is not the standard of care mainly because of a lack of evidence. The specific uncertainties for FFR adoption relate to a lack of evidence for FFR measurement in culprit arteries(23). When coronary resistance is reduced by vasodilator drugs, such as adenosine, the curvilinear relationship between coronary pressure and flow becomes approximately linear in the physiological range of blood pressure(232). Following STEMI, vascular injury may limit microvascular vasodilatation(127) and this may limit the validity of FFR which is by definition a hyperaemic index. In NSTEMI, the pathophysiology of the culprit artery is typically non-occlusive thrombotic plaque rupture and subendocardial infarction(16). Since FFR was measured in coronary arteries with normal blood flow, microvascular dysfunction may have been limited, transient or absent in the participants in this trial(129). The post-hoc analysis of medically stabilised ACS patients in the FAME trial also supports the validity of FFR.

A further area of uncertainty that was addressed in this trial relates to the management of NSTEMI patients with non-obstructive culprit lesions and potentially rupture-prone non-culprit lesions. Stenting to seal a non-flow limiting ruptured coronary plaque might reduce the risk of recurrent MI. Alternatively, optimal medical therapy might suffice and unnecessary stenting can be harmful (e.g. stent thrombosis, restenosis). The likelihood of MI increases with coronary stenosis severity and revascularisation guided by FFR reduces this risk in stable patients(119, 233). Whether FFR-guided management has prognostic benefits in ACS patients is uncertain and controversial. On the one hand, a reduction in revascularisation may reduce procedure-related MI. On the other hand, the risk of spontaneous MI might increase in the longer term in non-revascularised patients since plaque with rupture-prone biology may be non-flow limiting ($\text{FFR} > 0.80$). In our trial, 4 of the 10 patients with spontaneous MACE in the FFR group had an initial treatment plan for PCI in a culprit artery changed to medical therapy based on an $\text{FFR} > 0.80$. The spontaneous MACE events

in these patients occurred later during follow-up (3 - 11 months) in keeping with remodelling in the culprit artery and late spontaneous MI rather than a false-negative FFR result. The FFR results in the other patients with spontaneous MACE in the FFR group did not influence the initial management of these patients based on angiography alone implying the FFR strategy was not associated with the MACE events. In the FAME trial, nearly one third of participants in the FAME trial had a history of recent MI(126).

The potential for FFR disclosure to impact on physicians' treatment decisions in patients with recent unstable coronary disease is also uncertain(82). We found that FFR disclosure changed the treatment plan in over one in five patients with a reduction in revascularisation on a patient basis. However, late spontaneous MACE tended to be more common in the FFR-group, calling into question the longer term safety of an FFR-guided change from PCI to medical therapy in culprit arteries. These observations place emphasis on the need for a larger trial with a design that is informed by these results and powered to definitively assess health outcomes and cost-effectiveness.

The FAMOUS-NSTEMI trial differed from recent trials of FFR-guided management (DEFER,(228) FAME,(119) FAME-2,(229) and RIPCORDER(230)) in a number of important ways. Firstly, the primary diagnosis of the patients differed between the trials. DEFER, FAME and FAME-2 trials enrolled patients with stable coronary artery disease. In FAME, NSTEMI patients were included within 5 days of the index event provided the peak creatine kinase was less than 1000 U per litre. In FAME-2, patients with Canadian Cardiovascular Society angina class IV or an NSTEMI were only included if the symptoms had been controlled for more than 7 days. Secondly, the treatment strategies in these trials were not the same. In DEFER, FAME, and FAME-2, the patients were selected for PCI whereas FAMOUS patients were randomised upstream at an earlier stage in the treatment pathway when all treatment options were possible, including medical therapy, PCI and CABG. Thirdly, the angiographic criteria for FFR measurement differed between the trials. In the FAME trials, FFR was measured in stenoses assessed visually to be at least intermediate ($\geq 50\%$ reference diameter) in severity whereas in FAMOUS even very mild narrowings ($\geq 30\%$ reference diameter) were included. The characteristics of the participants in the FAMOUS trial were similar to those of other ACS trials, such as TIMACS(223) (e.g. 80% of participants in both trials had an ischaemic ECG). Finally, compared with standard care, health outcomes were improved by FFR-guided management

in the FAME trials whereas in FAMOUS, MI events were different and overall MACE were similar at 12 months.

Balancing against the potential benefits, use of a diagnostic coronary guidewire may come at the expense of cost and potential harm, including procedure-related coronary dissections. In this study, 2 coronary artery dissections were due to pressure wire instrumentation, as attributed by an independent clinical event committee which reviewed the angiograms. In the RIPCORD study(230), in which all coronary arteries were instrumented, 3 clinically important complications attributable to the pressure wire occurred in 200 patients.

In the angiography-guided group, the proportion of patients revascularised at baseline (86.8%, Table 4) was lower than the proportion of patients with an angiographically significant stenosis (96.6%, Table xx). By contrast, in the FFR-guided group, the proportion of patients with at least one physiologically-significant lesion ($\text{FFR} \leq 0.80$; 80.7%, Table 4) and the rate of revascularisation at baseline (81.7%, Table 4) were similar. In the sample size calculated we had anticipated a 15% difference in medical management between the randomised groups. The smaller actual difference (10.1%, Table 5) could be in part be explained by the lower than expected rate of revascularisation in the angiographic control group.

The rate of change of the initial treatment plan in our trial was lower than in other studies(119, 229, 230). This discrepancy is explained by the lower rate of lesion re-classification by FFR disclosure in patients with very mild ($<50\%$) or very severe ($>90\%$) lesions (Figure 15). Lesions at the extremes of coronary stenosis severity were included by design in order to assess the diagnostic impact of FFR across the full range of stenosis severities. The relationship between lesion severity and the health economic value of the FFR-guided strategy should inform whether this strategy has more economic value within an intermediate range of coronary stenosis severities (e.g. 50 - 90%). The health economic implications of this trial will be assessed in a future planned analysis.(231)

3.7 Limitations

The randomised participants in this trial were included because the cardiologist believed coronary instrumentation with the pressure wire was feasible, but this decision is subjective and some patients may not have been included due to operator preference. Even though some features of severe coronary disease

were exclusion criteria (e.g. a severely calcified coronary artery), some patients with severe coronary disease were still included supporting generalisability of the trial findings. For example, 6.6% of the participants were referred for CABG. 19% of the participants underwent angiography 5 or more days from the index episode of myocardial ischaemia. This time interval is explained by clinical service pressures that delayed access to the catheter laboratory in some of the hospitals in this trial.

Most of the participants in our trial received clopidogrel whereas ticagrelor, which improves cardiovascular outcomes in ACS patients compared to clopidogrel, is now recommended in NSTEMI patients (234). We have reported the cardiologists' visual interpretation of the angiogram as actually performed in the study participants. A quantitative coronary analysis by blinded observers is currently ongoing.

Our study was designed (but not powered) to assess between-group differences in health outcomes. There are too few cardiac events to draw firm conclusions and the prognostic significance of FFR-guided management in patients with optimal dual anti-platelet therapy should be further assessed in a larger trial with longer term follow-up.

3.8 Conclusions

The FAMOUS-NSTEMI trial provides information on the feasibility, safety, and clinical utility of a routine physiological approach to guide the management of NSTEMI patients. We have shown that compared with angiography-guided standard care, routine FFR measurement is feasible and safe, and FFR disclosure resulted in a change in treatment plan in more than one fifth of patients and revascularisation was reduced overall. There were no differences in health outcomes and quality of life between the randomised groups. In the FFR group, procedure-related MI tended to be reduced but spontaneous MACE during follow-up tended to be more common during 12 months follow-up. A large randomised trial is needed to definitively assess the cost-effectiveness of an FFR-guided management strategy in invasively managed NSTEMI patients.

Chapter 5

Assessment of Fractional Flow Reserve in Patients with Recent Non-ST segment Myocardial Infarction: A Comparative Study with 3 Tesla Stress Perfusion Cardiac Magnetic Resonance Imaging

Summary

Background

The use of fractional flow reserve in acute coronary syndromes is controversial. We report the findings of a cardiac magnetic resonance (CMR) study to assess the diagnostic accuracy of fractional flow reserve compared to 3.0 Tesla stress CMR perfusion in patients with a recent acute non-ST segment myocardial infarction (NSTEMI).

Methods

106 patients with NSTEMI who had been referred for early invasive management were included from 2 centers. FFR was measured in all major patent epicardial coronary arteries with a visual stenosis estimated at $\geq 30\%$ and if PCI was performed, an FFR assessment was repeated. Myocardial perfusion was assessed with stress perfusion CMR at 3.0 Tesla with intravenous adenosine (140 $\mu\text{g}/\text{kg}/\text{min}$) by trained observers blinded to the FFR results.

Results

Mean age was 56.7 ± 9.8 years. 82.6% were male. Mean time from FFR evaluation to CMR was 6.1 ± 3.1 days. The mean \pm SD left ventricular ejection fraction was $58.2 \pm 9.1\%$. Mean infarct size was $5.4 \pm 7.1\%$ and mean troponin concentration was $5.2 \pm 9.2 \mu\text{g}/\text{L}$. 1696 myocardial segments were analyzed and 32 segments were excluded from the analysis due to poor image quality.

There were 34 fixed and 160 inducible segmental perfusion defects. There was a negative correlation between the number of segments with a perfusion abnormality and FFR ($r = -0.77$, $p < 0.0001$).

The overall sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for $FFR \leq 0.8$ were 91.4%, 92.2%, 76% and 97% respectively. Diagnostic accuracy was 92%. The PPV and NPV of FFR for flow-limiting coronary artery disease ($FFR \leq 0.8$) in NSTEMI patients ($n=21$) who underwent perfusion CMR before invasive angiography were 92% and 93%, respectively. ROC analysis indicated that the optimal cut off value of FFR for demonstrating reversible ischaemia on CMR was ≤ 0.805 (AUC 0.94 (0.9-0.99), $p < 0.0001$).

Conclusion

FFR in patients with recent NSTEMI showed high concordance with myocardial perfusion in matched territories as revealed by 3.0 Tesla stress perfusion CMR.

4.1 Introduction

Fractional flow reserve (FFR) has an established role in guiding percutaneous coronary intervention (PCI) in stable coronary artery disease. In this setting, the use of FFR has been associated with improved long-term outcomes and reduced healthcare costs compared with angiographic-based strategies(119). Rates of urgent revascularization are reduced when compared with contemporary medical therapy(229). The validity of FFR is predicated on the ability to produce maximal hyperemia to achieve a linear relationship between pressure and flow(121). Maximal hyperemia may be less readily achieved in patients with recent MI because of microvascular dysfunction(128). Evidence on the potential diagnostic accuracy of FFR in patients with a recent acute coronary syndrome (ACS) is lacking.

In primary PCI for acute ST-elevation myocardial infarction (STEMI), FFR values are influenced and may reflect severe microvascular dysfunction in the territory of reperfused culprit artery(235, 236). The natural history of NSTEMI is different with most patients who are medically-stabilized presenting without coronary occlusion. In these patients, the microcirculation may have recovered and stabilized sufficient vasodilator capacity that FFR may be a valid measure of lesion-level flow. Recent clinical studies support the notion that contemporary FFR thresholds retain diagnostic accuracy amongst medically stabilized MI patients(125, 126, 132). For example, FFR correctly identified inducible ischemia on SPECT in 57 patients >6 days after MI(118) and in a follow-up study of 124 ACS patients, deferring revascularization in lesions with an $\text{FFR} \geq 0.75$ was safe(237). Based on invasive measurement of coronary vasodilator capacity (resistive reserve ratio, RRR) we found that patients with stable

angina and NSTEMI have a similar vasodilator reserve (129). Thus although recent studies are informative, more data concerning the validity of FFR in NSTEMI are needed.

We conducted in order to assess the relationships between invasively measured FFR and myocardial perfusion with cardiac magnetic resonance at 3.0 Tesla CMR. The purpose of this study was to examine the ability of FFR to predict reversible ischaemia when compared to a non-invasive gold standard in a large cohort of medically stabilized NSTEMI patients.

4.2 Methods

4.2.1 Study Population

106 patients were enrolled between November 2011 and June 2013 from two of the participating hospitals in the vicinity of the CMR center. One of the hospitals was a non-academic regional hospital and the other was an academic cardiothoracic center. The CMR study population consisted of patients with recent NSTEMI who had been referred for early invasive management guided by coronary angiography (NCT02073422). Exclusion criteria included coronary artery bypass graft (CABG) surgery, severe valvular heart disease and standard contraindications for CMR. Patients were scheduled for a pharmacological stress perfusion CMR scan at 3.0 Tesla following discharge from hospital. CMR was also performed in a subset of patients who had been discharged from hospital for early urgent out-patient coronary angiography/PCI.

The protocol was approved by the regional ethics committee and the study was undertaken in

accordance with the Declaration of Helsinki. All of the participants gave written informed consent.

4.2.2 CMR analysis

Higher field (3.0 Tesla) CMR was adopted as a reference method for assessing myocardial perfusion, as well as function and infarction(239). Heart imaging was carried out on a Siemens MAGNETOM Verio (Erlangen, Germany) 3.0 Tesla scanner with an 8-element phased array cardiac surface coil. The CMR protocol included assessment of left ventricular function using Steady State Free Precession (SSFP), myocardial infarction using late gadolinium enhancement (LGE), and myocardial perfusion was assessed by first-pass dynamic contrast-enhanced CMR (DCE-CMR).

Cine SSFP images with two-fold accelerated parallel imaging (GRAPPA) were acquired in a stack of short-axis views of the LV. Imaging parameters were: repetition time (TR) 3.4 ms, echo time (TE) 1.51 ms, flip angle (FA) 50°, typical field of view (FOV) (340 x 286)mm², matrix 256 x 216, slice thickness 7 mm, slice gap 3 mm, receiver bandwidth (BW) 977 Hz/px, 25 cardiac phases.

For perfusion, DCE-CMR was acquired in basal, mid-ventricular, and apical short axis slices during the first pass of 0.05 ml/kg of a 1-molar gadolinium based contrast agent (Gadovist, Bayer) injected with a power injector at a flow rate of 4mls/s.

Hyperaemia was achieved with an intravenous infusion of adenosine at 140 µg/kg/min for 3-4 minutes. All patients had desisted from caffeine for at least 12 hours prior to the scan and had otherwise complied with their standard medication.

DCE-CMR was performed with a fast gradient echo sequence with non-selective saturation recovery preparation pulse ($T_{SR} = 100\text{ms}$) and two-fold acceleration (GRAPPA). Perfusion sequence readout parameters were: TR/TE/FA = 2.4 ms/1.07 ms/ 12° ; FOV (340-400 x 340-400 mm²); matrix 160 x 120; BW = 651 Hz/px. Slice thickness was 8 mm, with 8 mm gap.

Rest perfusion imaging was acquired using the same DCE-CMR protocol 15 min after the stress scan with the administration of 0.05 ml/kg contrast agent (Gadovist, Bayer).

LGE CMR was performed with a T1-weighted segmented gradient-echo phase-sensitive inversion-recovery (GRE PSIR) sequence [10], with following parameters: TE/TR/FA = 760 ms/1.56 ms/ 20° . The inversion time (TI) was adjusted for optimal suppression of signal from normal myocardium (TI~340ms). Typical FOV was (350 x 262)mm², matrix 256 x 192, slice thickness 7 mm, slice gap 2.8 mm, and BW = 465 Hz/px. Images were collected 15-20 minutes after the last injection of contrast.

4.2.3 Analysis of stress/rest perfusion CMR:

Stress and rest perfusion CMR images were analyzed side-by-side using dedicated software (Argus Dynamic Signal, Siemens, Erlangen, Germany). The stress and rest myocardial perfusion scans were viewed simultaneously. The perfusion scans were visually assessed for normal and abnormal myocardial hypoperfusion and segments with abnormal perfusion were assigned to coronary territories using the American Heart Association coronary arterial 16-segment

model(224, 225). In cases of disagreement between observers, a third blinded observer adjudicated' and the observers also prospectively evaluated image quality. Two patients were excluded due to poor image quality.

A myocardial perfusion abnormality at rest and/or during pharmacological stress was classified as significant according to the presence of reduced perfusion in 2 segments of a 32 segment model (16-segment AHA model divided into sub-endocardial and sub-epicardial layers) i.e.: > 60 degrees in either the basal or the mid-ventricular slices or > 90 degrees in the apical slice or any transmural defect or two adjacent slices(225).

4.2.4 Invasive Coronary Angiography and Coronary Pressure Wire

All patients received an initial intravenous bolus of 5000 units of unfractionated heparin with an additional bolus of heparin as required to maintain an activated clotting time of 250 seconds. All patients had been pre-treated with aspirin and clopidogrel. A 6F coronary guiding catheter was used routinely and 200 µg of intracoronary nitroglycerin was administered during left and right coronary angiography. A 0.014" coronary pressure-sensing guide wire was calibrated and then equalized to the guiding catheter pressure with the guidewire sensor placed in the aorta at the ostium of the coronary artery. The wire was then passed beyond the stenosis into the distal third of the vessel. Systemic hyperemia was then established using intravenous adenosine at a dose of 140mcg/kg/min. Myocardial FFR was taken as the ratio of distal coronary to proximal aortic pressure during steady state hyperemia. An $FFR \leq 0.8$ was used as a measure of stenosis significance. An FFR value of 0.5 was given to patients with an occluded or sub-totally occluded

vessel(220).

4.2.5 Safety

All patients were prospectively evaluated for safety, including in relation to intravenous adenosine administration and coronary instrumentation with the diagnostic guidewire. Adverse events were recorded by the clinical and research staff in an electronic case report form (e-CRF) administered by the Pharmacovigilance Service of the Robertson Centre for Biostatistics, a trials unit registered with the National Institute for Health Research (NIHR).

4.2.6 Diagnostic accuracy study methodology

This analysis was conducted according to Standards for Reporting of Diagnostic Accuracy(240) and the study was reported in accordance with established best practice.

4.3 Sample size calculation

In order to pre-determine the sample size, we estimated that at least 40% of the study participants would have an FFR value ≤ 0.80 at the time of the index procedure and approximately 20% of the participants would have functionally-significant residual obstructive coronary disease at the end of the procedure reflecting incomplete revascularization of non-culprit coronary lesions (potentially as part of a staged management plan or lesions that were not amenable to revascularization). We therefore estimated that the prevalence of regional perfusion defects overall by stress perfusion CMR will be 30%. Theoretically, there should be close to a 1:1 correspondence with an inducible perfusion abnormality on stress CMR and an FFR ≤ 0.80 . Assuming a true underlying agreement rate of 90% and only one artery studied per patient, a sample size of 104 patients would have approximately 85% power to exclude an agreement rate

below 80% based on a one-sided 95% confidence interval. In reality more than one artery could be studied on a per-patient basis, hence increasing the power further.

4.4 Results (Table 6 and 7).

Table 6

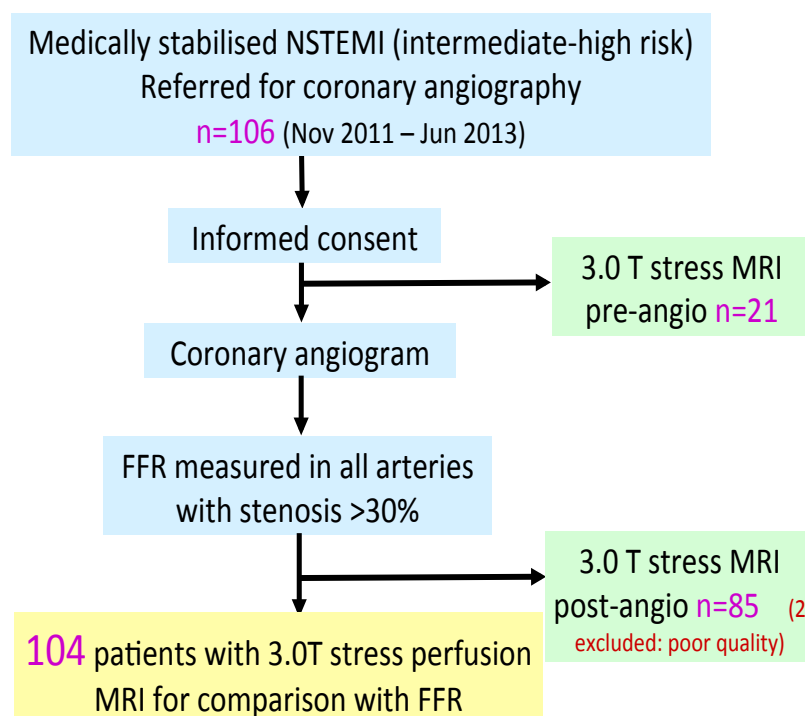
Variable	Value
Male (%)	86(82.6)
Age \pm SD	56.7 \pm 9.8
Diabetes (n/%)	13(12.6)
Smoker (n/%)	77(73.3)
Hypertension (n/%)	34(33)
Hypercholesterolaemia (n/%)	34(33)
Multivessel Disease (n/%)	55(52.9)
Previous PCI (n/%)	8(5.1)
Troponin μ g/l (\pm SD)	5.2 \pm 9.5
BMI (\pm SD)	29.17 \pm 4.7
GRACE (\pm SD)	163.6 \pm 35
Syntax Score (\pm SD)	12.4 \pm 7.7
Approach Score (\pm SD)	21.8 \pm 12.9
Treatment	
Medical (n)	27
PCI (n)	74
CABG (n)	3

BMI: Body Mass Index.

Of 251 medically stabilised NSTEMI patients who were randomized in the clinical trial from

Golden Jubilee National Hospital and Hairmyres hospital that participated in the CMR study, 106 (42.2%) were enrolled and had evaluable CMR data. A total of 1696 myocardial segments were available for analysis. 32 segments (2 patients) were excluded from the analysis due to non-diagnostic image quality so 1664 myocardial segments with evaluable perfusion CMR data were finally included. Of these, 793 segments were spatially matched with a coronary artery territory in which FFR was measured. The flow diagram for the CMR sub-study is shown in Figure 19. A typical clinical case including the CMR, angiography and FFR observations is shown in Figure 20.

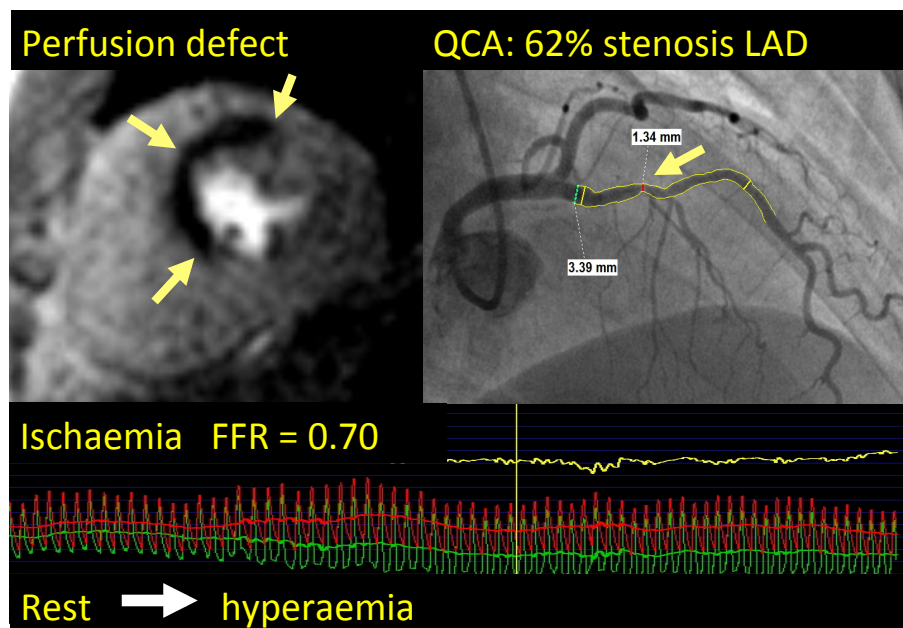
Figure 19



The demographics and characteristics of the NSTEMI patients are shown in Table 6. The mean age of the participants was 56.7 ± 9.8 years and 82.6% male. The mean time from FFR evaluation to CMR was 6.1 ± 3.1 days. The mean time from symptom onset to FFR evaluation was 4.4 ± 2.5 days.

Figure 20 – Comparison Between Stress CMR, FFR and coronary angiography.

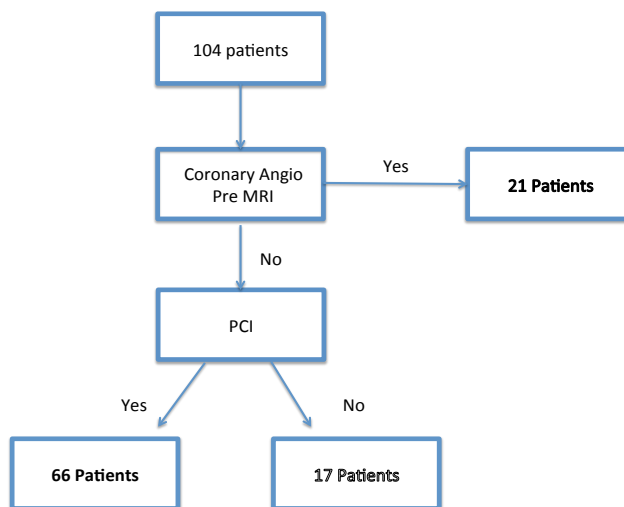
Anterior NSTEMI



A total of 21 NSTEMI patients had CMR examinations prior to coronary angiography/PCI and 83 patients had stress CMR following angiography/PCI (Figure 21). Of these 83 patients, 66

underwent PCI prior to the CMR. Of the 21 patients studied prior to coronary angiography, 8 patients underwent PCI and 1 patient went on to have CABG. The mean time interval between the CMR and FFR for this group was 6.6 ± 3.7 days. There were no adverse events related to intravenous adenosine infusion during either the invasive procedure for FFR or the stress perfusion CMR scan. No adverse events occurred in relation to coronary instrumentation with the diagnostic guidewire or with intravenous adenosine for FFR measurement.

Figure 21 – Breakdown of Patients Enrolled in the Study



4.4.1 Coronary Angiography and Physiology

A total of 168 coronary arteries were assessed, 96 (57%) in the infarct-related arteries and 72 (43%) in the non-infarct-related arteries. As reported by the interventional cardiologist in the

catheter laboratory, and based on all of the clinical information at the time of the procedure, the infarct-related artery was the left anterior descending coronary artery (LAD) in 47 NSTEMI patients, the left circumflex (LCx) in 17 patients, and the right coronary artery (RCA) in 18 patients. In one patient the identity of the culprit artery was unclear. The mean FFR for the population was 0.85 ± 0.13 .

4.4.2 CMR Findings (Table 7)

The mean \pm SD left ventricular ejection fraction was $58.2 \pm 9.1\%$ and the mean infarct size was $5.4 \pm 7.1\%$. There were 194 segments with a perfusion abnormality including 34 (18%) fixed and 160 (82%) inducible perfusion defects. The 160 inducible segmental perfusion defects occurred in 41 patients. 30 (73%) of these perfusion defects involved the infarct-related artery territory and 11 (27%) occurred in the non-infarct artery territory. There were 57 inducible perfusion defects (14 vessels) amongst patients imaged prior to and 103 defects (28 vessels) in those patients imaged following coronary angiography. There were 40 inducible transmural perfusion defects. Five (5%) patients had CMR evidence of perfusion abnormalities in multiple coronary artery territories. There was a negative correlation between the number of segments with an inducible perfusion defect and FFR ($r = -0.77$, $p < 0.0001$).

Table 7 – MRI and Clinical Variables

Variable	Value
LVEF (\pm SD)	58.2 \pm 9.1
LV Mass (\pm SD)	70.2 \pm 11.4
EDV (mls) (\pm SD)	90.4 \pm 15.9
ESV (mls) (\pm SD)	38.5 \pm 13.7
Infarct Size (\pm SD)	5.4 \pm 7.1
Infarct Related Artery (n)	LAD 47, Diagonal 2, LCx 17, OM 9, Ramus 3, RCA 18, Unclear 1
Non-Infarct Related Artery (n)	LAD 23, Diagonal 2, LCx 22, Ramus 2, RCA 20, LM 3
Coronary Stenosis Severity (%) (\pm SD)	50.3 \pm 21.4
Mean FFR (\pm SD)	0.85 \pm 0.13
Number of vessels with FFR \leq 0.8	41
Number of with FFR \leq 0.75	33

LVEF: Left Ventricular Ejection Fraction, EDV: End Diastolic Volume, ESV: End Systolic Volume

When looking only at the infarct-related culprit artery territory (n =89), there was a moderate negative correlation between the number of segments (n=113 segments) with an inducible perfusion abnormality on stress CMR and FFR ($r=-0.8$, $p<0.001$) When the analysis is restricted to coronary arteries with occlusive disease (i.e. arteries with an FFR allocation of 0.5 ascribed for severe, flow limiting stenosis/chronic occlusion), the correlation was moderate ($r=-0.69$, $p<0.0001$, n= 66 arteries, 59 segments).

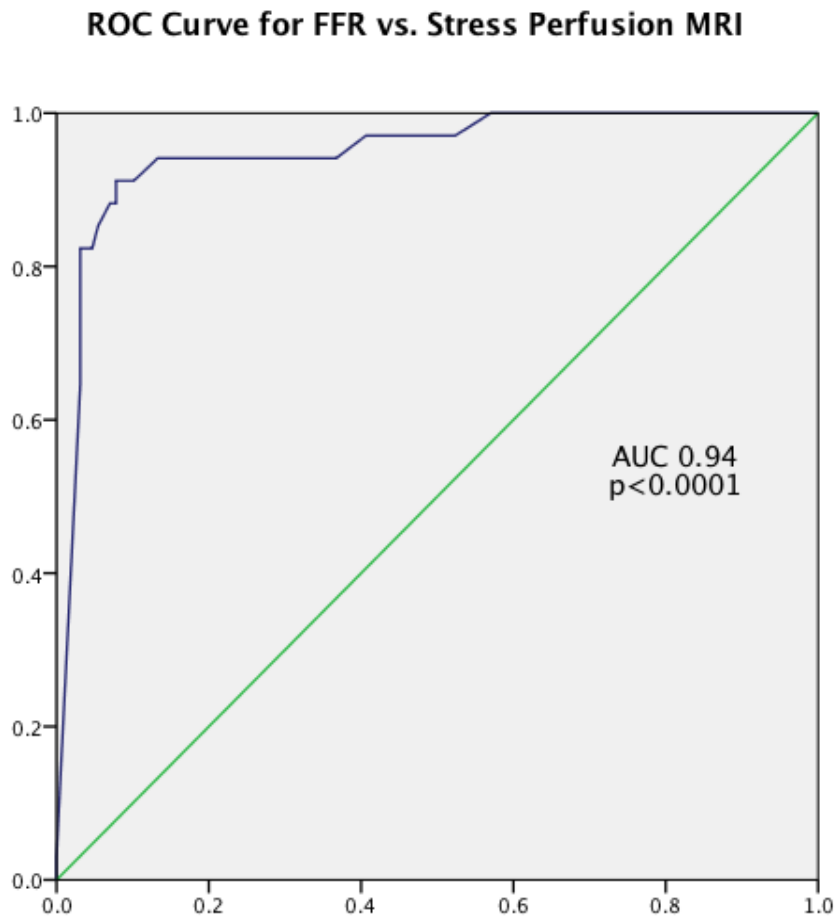
The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for $\text{FFR} \leq 0.8$ were 91.4%, 92.2%, 76%, and 97%, respectively. The diagnostic accuracy was

92%. The sensitivity, specificity, PPV and NPV for $\text{FFR} \leq 0.75$ was 88.2%, 95%, 83%, and 96%, respectively.

ROC analysis indicated that the AUC for FFR predicting an inducible perfusion defect on stress CMR was 0.94 (0.90-0.99), $p < 0.0001$ (Figure 22). The optimal cut off value was 0.805 and this was associated with a sensitivity of 91.2% and a specificity of 92.2%. Looking specifically at the infarct-related culprit artery the AUC was 0.91, $p < 0.001$. The optimal cut off value was again an FFR of 0.805 and this was associated with a sensitivity of 86% and a specificity of 95%.

On a per segment analysis, the FFR cut-off value of ≤ 0.8 was associated with an 87.2% sensitivity, 91.9% specificity, negative predictive value of 97% and positive predictive value of 65%.

Figure 22 – ROC Curve for FFR vs. Stress Perfusion MRI



4.4.3 CMR before vs. after angiography

NSTEMI patients who were had stress perfusion CMR before invasive angiography (n=21) had an altered clinical profile to those patients imaged after PCI/angiography. The mean Grace score was lower (GRACE score pre angio 140.0 ± 52.3 vs. 164.2 ± 34.8 [$p=0.63$]) as was the mean FFR

(mean FFR pre-angiography 0.7 ± 0.2 vs. mean FFR post-angiography 0.87 ± 0.13 , $p=0.004$). Other clinical characteristics for patients with CMR before vs. after angiography were similar, including patient age (57.8 ± 10.6 years vs. 56.4 ± 9.6 years; $p=0.6$), BMI (30.6 ± 4.6 kg/m² vs. 28.7 ± 4.7 kg/m²; $p=0.87$), time from CMR to FFR assessment (6.1 ± 3.7 days vs. 5.9 ± 3.1 days; $p=0.84$) or Syntax score (13.9 vs. Syntax 12.06 ; $p=0.51$).

The PPV of FFR for flow-limiting coronary artery disease ($FFR \leq 0.8$), compared with stress perfusion CMR perfusion before invasive angiography was higher when compared to patients' imaged after invasive management (sensitivity of 92%, specificity of 93.3%, PPV of 92% and a NPV 93%), and accuracy was otherwise similar.

4.4.4 Discordance Between FFR and CMR Evaluation of Ischaemia

There was discordance between FFR and CMR involving 63 segments with an almost equal distribution between the non-culprit (32 segments) and the culprit (29 segments) territories. These involved 21 coronary arterial territories. However, in 16 territories despite this discordance in individual segments, the diagnostic utility of FFR to identify inducible ischaemia was preserved.

4.5 Discussion

The most important finding of this study is the high diagnostic accuracy of FFR at established thresholds for lesion-level flow limitation when compared against myocardial perfusion revealed

by stress perfusion CMR at 3.0 Tesla. We have shown that as a diagnostic test for detecting flow-limiting coronary artery disease, the performance of FFR was excellent with an AUC of 0.94. Prior to our study, the validity of FFR and its established ischemic thresholds of 0.80 and 0.75 in patients with a medically stabilized NSTEMI was uncertain. The high prevalence of multivessel coronary disease and the impractical use of non-invasive tests in the acute setting support the theory that FFR might have potential diagnostic value in this population. Since the performance of FFR could rule-out the need for deferral of treatment in order to obtain a non-invasive stress test to assess the functional significance of bystander coronary disease, FFR has potential clinical utility in the context of a single diagnostic and therapeutic procedure in NSTEMI patients during urgent ad hoc invasive management.

4.5.1 Use of 3T CMR as Non-Invasive Reference Standard

Comparing FFR with a non invasive gold standard for diagnosing ischaemia is a point of contention within the medical literature (241, 242) particularly because FFR was originally compared with non-invasive imaging for its own validation. However, with the continued improvements in CMR imaging and with a lack of a clear gold standard for non-invasively diagnosing ischaemia, CMR was chosen as a reference standard to assess the accuracy of FFR

4.5.2 Concerns regarding the use of FFR to guide management in ACS

Culprit Arteries

In the setting of emergency primary PCI for acute STEMI severe microvascular injury precludes

maximal hyperemia such that FFR is not valid as a diagnostic test (235, 236, 243). In the NSTEMI setting, the nature of the microvascular injury is typically different since the culprit coronary artery remains patent with normal antegrade flow, which is the usual finding during invasive angiography¹³. In some NSTEMI patients, the natural history may involve intermittent coronary occlusion (e.g. due to vasospasm, thrombus burden), but typically the occlusion is transient. Furthermore, microvascular injury may also be transient such that initial measurements of FFR may be artificially elevated but following stabilisation of the coronary microcirculation, FFR reflects the true haemodynamic impact of the coronary stenosis. In our study, FFR was restricted by protocol to coronary arteries with normal flow, and in the case of CTOs or very severely obstructed arteries an FFR value of 0.5 was assigned. Furthermore, in NSTEMI patients' invasive angiography is generally performed on a sub-acute basis usually 24 hours or more after initial presentation during which time anti-thrombotic treatments are given. Theoretically, maximal coronary vasodilatation that is required to establish the critical linear relationship between pressure and flow necessary for the assessment of FFR (79) may still not be achieved. The attainment of maximal hyperemia is predicated on preserved microcirculatory function, since the distal coronary microcirculation is the major contributor to coronary vascular resistance. However, using cardiac positron emission tomography (PET), Uren and colleagues provided evidence of impaired microcirculatory function in the infarcted region compared with healthy controls up to 6 months following AMI (127). Thus, in patients with recent MI microvascular injury, stunning and oedema may result in a failure to achieve minimal resistance and FFR values may be falsely elevated (127). Tamita and colleagues highlighted this by demonstrating a higher post-PCI FFR in patients with STEMI compared with patients with stable angina despite similar intravascular ultrasound parameters. Patients with TIMI II flow also had a

higher FFR compared to those patients with TIMI III flow. Thus in patients with severe microvascular dysfunction the assessment of FFR may be unreliable.

We have demonstrated a good correlation between inducible ischaemia demonstrated on a non-invasive gold standard and FFR in the culprit artery of patients with NSTEMI. Furthermore we have shown excellent test accuracy with an AUC of 0.91, a sensitivity of 86% and specificity of 95%. Indeed the optimal cut off value for FFR was 0.8. This excellent concordance provides further evidence for the validity of FFR measurements in the culprit vessel of patients with recent NSTEMI and supports previous findings(125).

Non-Culprit Arteries

Several studies have clearly demonstrated altered blood flow patterns and impaired vasodilator response in territories remote from the culprit vessel (127, 244). As discussed above this could potentially have implications for the assessment of FFR in non-culprit vessels in patients presenting with ACS.

4.5.3 FFR thresholds in ACS

In patients with stable CAD, a myocardial $FFR \leq 0.80$ is an evidence-based physiological threshold indicative of lesion-level ischaemia due to obstructive CAD that may be amenable for revascularization (79). The original validation studies that determined the FFR threshold for ischemia were all performed in stable patients. However, there have been several studies that have aimed to establish and validate FFR thresholds for ischaemia in patients with ACS. In 48

stabilized patients with recent MI, Samady and colleagues compared FFR in the infarct-related artery to non-invasive findings using SPECT and myocardial contrast echocardiography (MCE). Patients had a mean time to angiography of 3.7 days. 73% of patients presented with STEMI. The group demonstrated that an FFR ≤ 0.75 had 91% sensitivity, 93% specificity and a diagnostic accuracy of 92% for detecting reversible ischaemia. They provided an optimal cut off FFR value of ≤ 0.78 for detecting reversible ischaemia using ROC analysis (125). Furthermore, Ebersberger and colleagues reported the findings of a similarly designed FFR vs. CMR study at 3.0 Tesla in 116 patients with stable angina. They demonstrated sensitivity, specificity, positive and negative predictive value of 89%, 95%, 87% and 96% respectively (241). Our data are in accordance with these findings and support the diagnostic utility of FFR in patients with NSTEMI in the culprit and non-culprit territories at 4 days after MI to identify reversible ischaemia.

Our findings are similar to those of Samady and colleagues and higher than the threshold originally put forward for patients with stable angina (245) and may reflect higher microvascular resistance in patients with recent NSTEMI compared with controls in line with recent observations by our group (129)

4.5.4 Current Evidence for Benefit of FFR in ACS

The FAME trial also included patients with NSTEMI/Unstable Angina(119, 126). FFR-guided revascularization was associated with a similar magnitude of treatment effect over angiography-guided PCI in patients with recent NSTEMI/UA compared to those with stable angina. However, the pooling of patients with unstable angina and NSTEMI, the lack of information on the timing of the index infarction or troponin values and risk stratification (e.g. with the GRACE

score) supported the case for further studies investigating the relationship between FFR and NSTEMI.(126).

Most data relating to FFR in NSTEMI thus far have been retrospective or observational. Potvin et al demonstrated that in 201 unselected patients presenting to the catheter laboratory the use of an FFR threshold of ≤ 0.75 was safe to allow deferral of stenting. However only 21 % of patients had a recent STEMI/NSTEMI and the use of FFR was not randomized or blinded. Thus although helpful, these studies were in relatively stable patients and not powered to detect any impact of FFR-guided management on health outcomes or to determine the clinical utility of FFR or optimal cut-off in patients with ACS.

Lopez-Palop et al have recently published the results of an observational non-randomized cohort of 107 NSTEMI patients who had FFR evaluation of non-culprit stenoses(246). They demonstrated no difference in outcome between patients who had revascularization deferred on the basis of FFR compared with those who underwent angiographically guided revascularization. In addition, Ntalianis et al evaluated the assessment of non-culprit stenoses in 26 patients with an acute NSTEMI (within 72 hours) and 126 patients with STEMI and showed that FFR values in the non-culprit vessel were unchanged when measured again approximately 5 weeks later(247). Thus the use of FFR to evaluate non-culprit stenoses has been shown to be reasonably accurate and reproducible in different NSTEMI populations, including from this analysis also.

The results from our study are in accordance with FAME(247) and provide further evidence of the validity of FFR in this population.

4.5.5 Potential Benefits of FFR guided stenting in patients with ACS

Contemporary guidelines recommend making revascularization decisions for culprit lesions in patients with convalescent STEMI and NSTEMI/UA in the same manner as stable angina. This strategy appears to improve symptoms and reduce rates of death and non-fatal MI at long-term follow-up (23). However, there has been discordance in the literature with some authors suggesting a lack of prognostic benefit of revascularization over modern medical therapy in NSTEMI (248). Current revascularization guidelines for stable angina recommend the use of non-invasive stress testing/FFR for lesions that are angiographically intermediate in severity(1, 249). However, this strategy, whilst appropriate in stable angina, is problematic in patients with NSTEMI not only because stress testing is not recommended but also because FFR has not been extensively validated in this population. Our data provide further evidence of the applicability of FFR in patients with recent NSTEMI in both the culprit and non-culprit vessels.

4.5.6 Discordance Between FFR and CMR

We observed discordance between FFR and CMR diagnosis of ischaemia in 63 MRI segments. However, this most commonly involved an isolated segment within an already ischaemic territory. As this did not meet the pre-specified CMR definition of ischaemia the diagnostic utility of FFR was preserved. Due to the small numbers, we could not define a relationship between discordance and timing of MRI/clinical presentation.

4.6 Limitations

A minority of the NSTEMI patients in our study had stress perfusion CMR before invasive management whereas the majority had CMR afterwards. This meant that a significant proportion of patients had revascularization prior to the CMR. However, CMR was performed on average 6 days after invasive management allowing time for microvascular dysfunction related to the PCI procedure (performed after FFR) to improve. Nevertheless, the time-interval between CMR and FFR, and PCI-related microvascular injury may be confounding factors for the FFR vs. perfusion CMR relationship.

Since many centers perform intervention on NSTEMI patients within 48 hours of presentation, the generalizability of our results is limited to patients who present within a similar time frame. However, since FFR was performed within 5 days of presentation to hospital and a pre-defined inclusion was that the patients must have pain within the last 5 days (or have had their NSTEMI in the last 72 hours) our data remain relevant.

We found evidence of a high sensitivity and a specificity of FFR for flow-limiting coronary disease, as revealed non-invasively by stress perfusion CMR. Our results are in keeping with established data (125, 241) but should be interpreted on the basis that the NSTEMI participants had a high pre-test likelihood of coronary artery disease. This fact is also relevant when considering the higher PPV of FFR for abnormal myocardial perfusion in patients undergoing CMR before invasive angiography and revascularization.

Whilst we have demonstrated excellent concordance between FFR and stress CMR, we should not expect one-to-one concordance between FFR and myocardial perfusion since fundamentally the tests are different. FFR is an invasive guidewire-based pressure-derived index of coronary blood flow that can be anatomically specified to individual coronary lesions with a readout displayed in real-time on a hemodynamic monitor. Perfusion MRI is non-invasive and provides information on myocardial perfusion based on dynamic changes in myocardial contrast kinetics and signal intensity in just a few heart beats. In clinical practice the signal changes are assessed visually. We have assumed spatial concordance for the coronary artery instrumented for FFR measurement and its distribution on the myocardial perfusion scan, but other biological factors may affect this relationship including subject-specific variations in coronary anatomy with respect to standard angiographic classifications (e.g. Coronary Artery Surgery Score (250) (CASS), DUKE Jeopardy (251) Score) and also coronary collateral supply.

4.7 Conclusion

This is the first study to date to examine the diagnostic accuracy of FFR in a reasonably large cohort of patients with recent NSTEMI vs. a high fidelity non-invasive reference method. Our results indicate that FFR and stress perfusion CMR at 3.0 Tesla were highly concordant and add further evidence for the utility of FFR in this population.

Chapter 6

Diagnostic Accuracy of 3.0 Tesla Magnetic Resonance T1 and T2 Mapping and T2W STIR Edema Imaging for the Infarct-Related Coronary Artery in NSTEMI

Summary

Background: Patients with recent non-ST elevation MI (NSTEMI) typically have heterogeneous infarct characteristics that may be difficult to assess clinically.

Methods and Results: We prospectively studied the diagnostic accuracy of two novel (T1, T2 mapping) and one established (T2-weighted short tau inversion recovery (STIR)) magnetic resonance imaging (MRI) methods for imaging the ischemic area-at-risk and myocardial salvage in 73 NSTEMI patients (mean age 57 ± 10 yrs, 78% male) at 3.0 TMRI within 6.5 ± 3.5 days of invasive management. The infarct-related territory was identified independently using a combination of angiographic, ECG and clinical findings. The presence/extent of infarction was assessed with late gadolinium enhancement imaging (Gadovist, 0.1 mmol/kg). Area-at-risk was independently assessed with native T1, T2 and T2W-STIR methods. The mean infarct size was $5.9 \pm 8.0\%$ of left ventricular mass. The area-at-risk T1 and T2 times were 1323 ± 68 ms and 57 ± 5 ms, respectively. The extent of area-at-risk (% of LV mass) estimated with T1 ($15.8 \pm 10.6\%$) and T2 maps ($16.0 \pm 11.8\%$) was similar ($p=0.838$), and moderately well correlated ($r=0.82$, $p<0.001$). Mean area-at-risk estimated with T2W-STIR ($7.8 \pm 11.6\%$) was lower than that estimated with T1 ($p<0.001$) or T2 maps ($p<0.001$). There were moderate correlations between area-at-risk estimated with T1 maps vs. T2W-STIR ($r=0.54$, $p<0.001$), and area-at-risk estimated with T2 maps vs. T2W-STIR ($r=0.46$, $p<0.001$). The diagnostic accuracies of T1 and T2 MRI for identification of the infarct related artery were similar ($p=0.125$) and both were superior to T2W-STIR ($p<0.001$).

Conclusions: In NSTEMI patients, T1 and T2 MRI mapping have higher diagnostic accuracy

than T2W-STIR for delineating acute myocardial injury, implying superior clinical utility.

5.1 Introduction

Following acute myocardial infarction cardiac MRI imaging techniques have been shown to estimate the ischaemic area at risk (AAR), that is, the myocardial perfusion bed directly affected by ischaemia due to the acute occlusion of a coronary artery (35). Furthermore, as a result of even transient ischaemia producing differences in the myocardial longitudinal (T1) and transverse (T2) relaxation times, newer techniques have shown improved sensitivity in identifying the culprit territory (47, 48). Dark-blood fat-suppressed (short tau inversion recovery, STIR) T2-weighted MRI methods (T2W STIR) are widely used for clinical and research purposes (37, 49, 252, 253). However, T2W STIR is prone to artifacts from motion, blood-tissue borders and coil sensitivity issues cause signal loss with depth of field(254, 255) and may lead to diagnostic uncertainty. Novel fast T1 and T2 parametric methods for mapping the area at risk have been described in patients with STEMI, typically a syndrome associated with large areas at risk and large, transmural myocardial injury. In these cohorts, both T1 and T2 mapping techniques demonstrated superior accuracy compared with T2W STIR(48, 54) Since edema persists for days or weeks after an acute ischaemic injury, STEMI patients have generally been studied following revascularisation, a time when potential benefit of identifying the AAR is limited. NSTEMI is a condition typified by smaller degrees of myocardial injury and non-occlusive culprit lesions. Compared with STEMI, the clinical utility of identifying the AAR in NSTEMI patients may be enhanced since NSTEMI is a more heterogeneous condition and MRI

can be performed prior to a decision to proceed to an invasive management strategy. However, data allowing direct comparison of T1/T2 mapping sequences and T2W STIR in NSTEMI, particularly at 3.0 Tesla, are lacking.

We performed a prospective study of medically stabilized NSTEMI patients referred for coronary angiography to compare the diagnostic accuracy of T1 and T2 mapping compared to dark blood edema imaging (T2W STIR) for detection of the infarct-related artery. We also compared these MRI methods for estimation of the ischaemic area at risk.

5.2 Methods

5.2.1 Patient population

Patients with a diagnosis of Type 1 NSTEMI (25) with at least one cardiac risk factor scheduled for early coronary angiography were prospectively recruited. Exclusion criteria represented standard contraindications to MRI, including metallic devices and severe kidney disease (an estimated glomerular filtration rate <30 ml/min/1.73 m²). The participants in this study had been enrolled in a clinical trial (ClinicalTrials.gov identifier:NCT02073422). All patients provided written, informed consent. The local ethics board approved the study. Pharmacological management of patients reflected contemporary guidelines including treatment with dual anti platelet therapy, an HMGCo-enzyme inhibitor and a beta-blocker (23).

5.2.2 MRI Acquisition

MRI was performed on a Siemens MAGNETO Verio (Erlangen, Germany) 3.0 T scanner with an 8-element phased-array cardiac surface coil. The MRI protocol included steady state free precession (SSFP) cine MRI, T1 and T2 parametric maps, as well as T2W STIR. Cine SSFP images with two-fold accelerated parallel imaging (GRAPPA) were acquired in a stack of short-axis views of the LV. Imaging parameters were: repetition time (TR) 3.4 ms, echo time (TE) 1.51 ms, flip angle (FA) 50°, typical field of view (FOV) (340 x 286)mm², matrix 256 x 216, slice thickness 7 mm, slice gap 3 mm, receiver bandwidth (BW) 977 Hz/px, 25 cardiac phases.

LGE CMR was performed with a T1-weighted segmented gradient-echo phase-sensitive inversion-recovery (GRE PSIR) sequence [10], with following parameters: TE/TR/FA = 760 ms/1.56 ms/20°. The inversion time (TI) was adjusted for optimal suppression of signal from normal myocardium (TI~340ms). Typical FOV was (350 x 262)mm², matrix 256 x 192, slice thickness 7 mm, slice gap 2.8 mm, and BW = 465 Hz/px. Images were collected 10 to 15 minutes after the administration of 0.1 mmol/kg contrast agent (Gadovist, Bayer).

The ECG-gated single shot modified Look-Locker Inversion Recovery (MOLLI) method was used to measure myocardial longitudinal relaxation times (T1)(55, 256). The MOLLI parameters included a T1 start of 100 ms, an increment of 80 ms and a trigger delay of 160 ms. The protocol included GRAPPA acceleration factor of 2. Following pixel-wise T1 fitting, T1 (ms) was displayed on a quantitative colour scaled map.

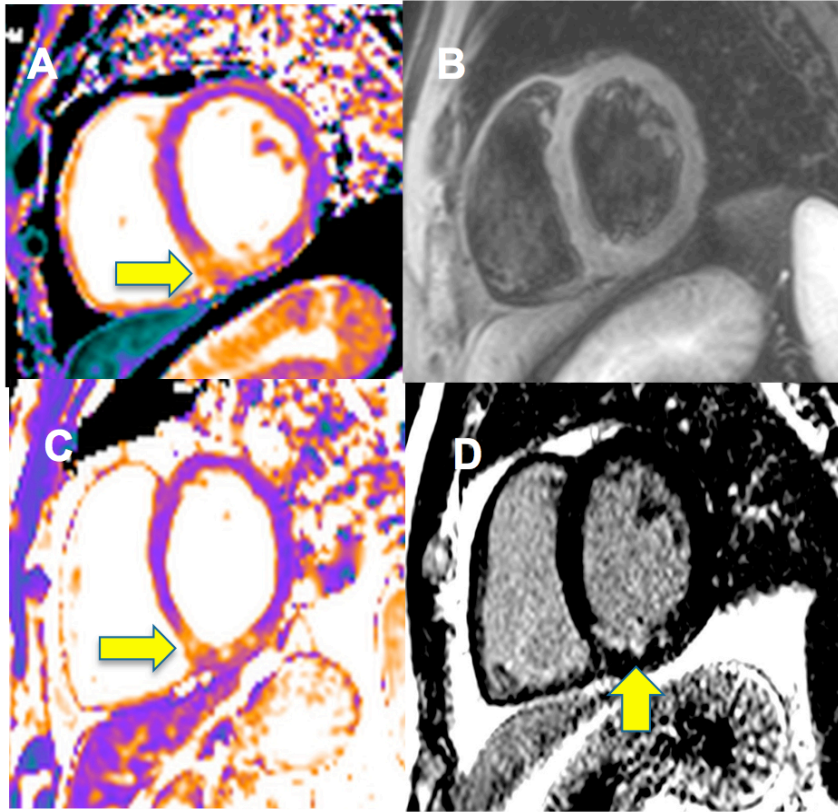
Myocardial transverse (T2) relaxation times were estimated using a T2 mapping technique that

involved a T2 prepared TrueFISP pulse sequence to produce single-shot T2 prepared images, each with different T2 preparation times (257). The T2 prepared TrueFISP images were acquired at intervals of at least 3 R-R intervals to allow for sufficient magnetisation recovery in between acquisitions. Motion correction was enabled to prevent misregistration between images. T2 was estimated by pixel-wise fitting assuming a mono-exponential signal decay and a colour scaled motion corrected myocardial T2 map was then generated. For both T1 and T2 maps, an algorithm for motion correction based on previous work was applied prior to curve fitting (258).

The breath hold black blood triple inversion recovery sequence (T2W STIR) involves a pair of selective and non-selective 180 degree inversions pulses to null the blood pool signal followed by a third inversion pulse (STIR) to null the fat signal(49). Surface coil intensity correction was routinely performed with pre scan normalisation and slice-related shimming as appropriate. Typical imaging parameters were TE/TR/FA = 2RR intervals /47ms/180, with 310 Hz/pixel bandwidth and turbo factor 15. In-plane spatial resolution was 2.2 x 1.4 mm (with acquisition matrix of 151 x 256, GRAPPA = 2), and slice thickness was 6-mm. Short axis left ventricular views were sequentially acquired with T1/T2 parametric maps and T2W STIR matched to the same slice position. We obtained 3 slices, basal, mid and apical. Sample images are shown in Figure 23.

Figure 23- Clinical Vignette - T1 and T2 Maps vs. T2W STIR imaging

Clinical Case: Inferior NSTEMI. RCA lesion. MRI: Edema shown on T1 and T2 maps. No edema on T2 STIR.



Yellow arrow showing myocardial injury.
A: T2 Map, B: T2 STIR, C: T1 Map, D: LGE

MRI findings in a 62 years old male patient with acute NSTEMI (A=T2 Map, B= T2W STIR, C= T1 Map, D=Late Gadolinium Enhancement). Inferior subendocardial infarction, as revealed by LGE, corresponds with transmural edema revealed with T1 and T2 maps but this is not seen with T2W STIR.

5.2.3 MRI Image analysis

Anonymised images were analysed in a random order on a Siemens workstation by 2 MRI trained cardiologists with > 3 years experience with imaging myocardial edema. An image analyst coordinated data management to ensure blinded analysis. A third MRI trained cardiologist as well as an MRI trained technician performed quantitative assessments of infarct area and area-at-risk as determined by both T1 and T2 maps.

Two MRI trained cardiologists who were blind to the patients' clinical presentation reviewed Hyperintense zones on T1- and T2-weighted MRI images independently. Each observer assessed for the presence/absence of edema in each short axis slice and ascribed it to a segment in accordance with the 16-segment model of the American Heart Association. A third observer resolved discordance between cardiologists. Each observer was also asked to assign a culprit coronary arterial territory for each patient based on each edema imaging modality. In addition, each observer was asked to categorize overall image quality (non-diagnostic, poor, adequate, good, or excellent) as well as to comment on the presence/absence of artifacts for each edema imaging sequence. An artifact was only recorded if there was concordance in 2 out of the 3 observers.

The jeopardized left ventricular area at risk was defined as the percentage of left ventricular area delineated by the hyper intense zone on T1 and T2 images. The signal intensity threshold indicating edema was set at 2 standard deviations (SD) above the mean intensity of reference ROI placed in remote unaffected myocardium. Myocardial tissue with a signal intensity at least 2

SD above the mean signal obtained in the remote non-infarcted myocardium was considered the area at risk(44, 66). Myocardial salvage was calculated by subtraction of percent infarct size from percent area at risk(44). The extent of infarct scar was delineated as an area of myocardial enhancement (cm^2) mapped on LGE images, using a signal intensity threshold of >5 standard deviations (SD) above remote region, and expressed as a percentage of total LV mass(259, 260). MVO was defined as a dark zone present within an area of gadolinium enhancement. Infarct regions with evidence of MVO were included within the infarct area, and MVO area was also recorded individually as a percentage of total LV mass.

5.2.4 Angiographic Analysis

The attending interventional cardiologist using a combination of clinical history, ECG and coronary angiographic findings identified the culprit artery. The Alberta Provincial Project for outcome Assessment in Coronary Heart Disease (APPROACH) lesion score was used to provide estimates of the AAR(59). Culprit artery assignment was independently analysed and verified by an accredited interventional cardiologist (MMC).

5.2.5 Statistical analyses

Statistical analyses were carried out using IBM SPSS Statistics software, version 21.0 (Armonk, USA). Normality was tested with the Shapiro-Wilk test. All results are given in a format of mean \pm SD, unless otherwise stated. Correlations between AAR quantified with T1/T2maps and T2W STIR, APPROACH lesion scores were tested by Pearson or Spearman's methods as

appropriate. Comparisons of normally distributed continuous data between T1/T2 maps and T2W STIR were undertaken using a Student *t* test. Between- group comparisons of non-normally distributed data were performed with a Mann Whitney test. The level of agreement between AAR quantified with T1/T2 maps and T2W STIR was assessed using Bland-Altman plots and 95% limits of agreement. The 95% limits of agreement were calculated using the mean difference between AAR quantified by the two imaging modalities ± 2 SD of these differences, and contained approximately 95% of all such differences. The McNemar exact test was used to compare diagnostic accuracy of the T1, T2 and T2W STIR sequences in identifying the infarct-related artery, when compared to current gold-standard method of coronary angiography. An inter-observer agreement reliability analysis, using the Kappa statistic (κ), was performed to determine consistency of infarct-related artery diagnosis among observers. To assess reproducibility, quantitative assessment of the area at risk on T1 and T2 maps was assessed by a second observer on a subset of 18 patients. The level of agreement between the two observers assessing the area at risk on T1 and T2 maps was assessed using Bland Altman plots and 95% limits of agreement.

5.3 Results

5.3.1 Patient characteristics (Table 8)

Between February 2012 and May 2013, we recruited seventy-three NSTEMI patients (mean age 57 ± 10 years, 78% male) who underwent cardiac MRI within 6.5 ± 3.49 days of invasive management. All patients fulfilled the diagnostic criteria for acute NSTEMI and the infarct-related coronary arteries were identified by clinical criteria including the ECG and coronary

angiography. Patient demographics and clinical characteristics are provided in table 8. The mean GRACE score at hospital was 156 ± 37.25 . Overall, 27.4% of patients were imaged prior to, and 72.6% following coronary angiography. Angiographic characteristics, in particular, the infarct related artery assignments are provided in table 8. Sixty three percent of the study population underwent percutaneous coronary intervention.

5.3.2 Cardiac MRI findings

The cardiac MRI findings are summarized in Tables 9 and 10. Of 26 patients (35.6%) without evidence of LGE, 16 (61.5%) had evidence of edema. The mean infarct size as a percentage of LV volume was $5.9 \pm 8.0\%$. There was no evidence of edema using two out of the three imaging methods in 10 (13.6%) patients and MVO was present in 10 patients (14%). The mean left ventricular ejection fraction was $57 \pm 12\%$. On average, 3 short axis slices were available for native T1, T2 maps and T2 STIR images. 83.3% of patients had either excellent or good image quality. No patient was excluded due to poor image quality.

There were significantly more artifacts with T2 STIR (57.1% images) compared with T1 maps (14.4%) and T2 maps (3.7% images), $p < 0.0001$. When comparing the two parametric mapping techniques directly, there was significantly more artifacts with T1 maps compared with T2 maps ($p < 0.0001$)

Table 8 – Baseline Characteristics of Cohort

Characteristic	Value
	57±10
Age, years	
	57(78)
Male, n (%)	
	28.7±4.8
Body Mass Index, kg/m ²	
	52(72.2)
Smoker, n (%)	
	25(34.7)
Hypertension, n (%)	
	23 (32.4)
Hyperlipidaemia, n (%)	
	9 (12.3)
Diabetes, n (%)	
	6 (8.2)
Previous percutaneous coronary intervention, n (%)	
	156±37.25
GRACE score	
	0.92 (0.2,5.3)
Troponin, mg/dl	
<i>Infarct Related Artery</i>	
Left Anterior Descending, n (%)	33(45)
Circumflex, n (%)	23(32)
Right Coronary, n (%)	17(23)
<i>Treatment Strategies</i>	
Medical Therapy only, n (%)	21(28.7)
Coronary Artery Bypass Surgery, n (%)	6(8.2)
Percutaneous Coronary intervention, n (%)	46(63)
APPROACH Lesion Score, % left Ventricular mass	23.45±12.6

Table 9 – MRI Findings

MRI parameter	Value
<i>Left Ventricular dimensions and function, mean±SD</i>	
Left Ventricular ejection fraction, %	57±12
End-diastolic volume index, ml/m ²	93±17
End-systolic volume index, ml/m ²	41±16
Left Ventricular mass index, g/m ²	71±10
<i>Late gadolinium enhancement</i>	
Patients with evidence of LGE, n (%)	48(66)
Mean ±SD acute infarct size,% of LV mass	5.9±8.0
Microvascular Obstruction, n(%)	10(14)

Table 10 – Values in Remote and Injured Zones with Different Edema Imaging Modalities

	Remote	Edema	P
T1 time, ms	1152±43	1323±68	<0.001
T2 time, ms	45±3	57±5	<0.001
T2W-STIR, arbitrary units	90±25	146±55	<0.001

The mean signal intensity (SI) of remote and injured myocardium is shown in Table 10 for each of the imaging methods. The measurements from acutely ischemic regions were higher compared to remote, unaffected myocardium for each method (T1 maps edema: 1323±68 msec vs. no edema 1152±43 msec, $P<0.001$; T2 map edema: 57±5 msec vs. no edema 45±3 msec, $P<0.001$; T2W STIR edema 146±55 vs. no edema 90±25, $P<0.001$).

Figure 24 and 25: T1 and T2 values (m/sec) in remote territory and in the injury zone (IZ)

Figure 24

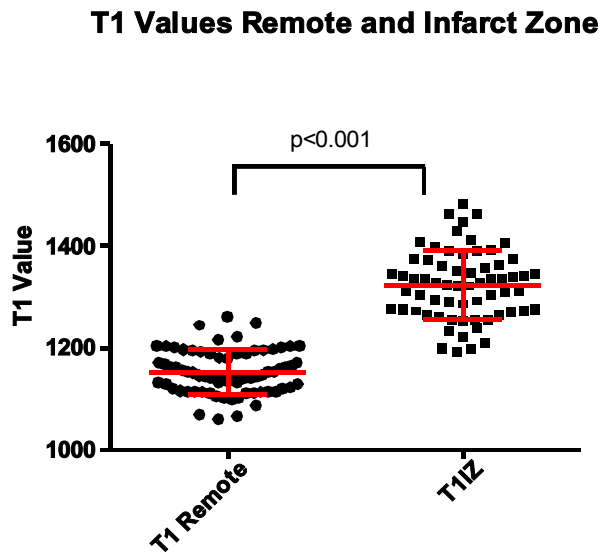
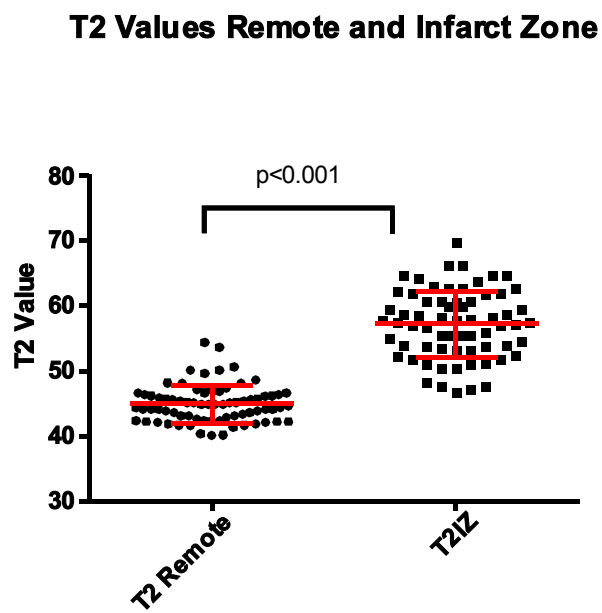


Figure 25



For area-at-risk estimated by 2 independent observers using T1 mapping there was good correlation between observer 1 and observer 2 ($r^2=99.7\%$). The 95% limits of agreement were -1.76 and 1.63 and there was no evidence of bias (0.25). For area at risk estimated by T2 mapping between these observers, there was good correlation ($r^2=98.9\%$), with 95% limits of agreement being -2.98 and 3.36 and no evidence of bias (0.19).

5.3.4 Detection of Acute Edema by T1, T2 maps and T2 STIR.

Table 11

T2 map				
IRA territory identified		Correct (n=56)	Incorrect (n=17)	
T1 map	Correct (n=52)	52	0	52 (71%)
	Incorrect (n=21)	4	17	21 (29%)
		56 (77%)	17 (23%)	$P=0.13$
T2 STIR map				
IRA territory identified		Correct (n=32)	Incorrect (n=41)	
T1 map	Correct (n=52)	31	21	52 (71%)
	Incorrect (n=21)	1	20	21 (29%)
		32 (44%)	41 (56%)	$P<0.001$
T2 STIR map				
IRA territory identified		Correct (n=32)	Incorrect (n=41)	
T2 map	Correct (n=56)	31	25	56 (77%)
	Incorrect (n=17)	1	16	17 (23%)
		32 (44%)	41 (56%)	$P<0.001$

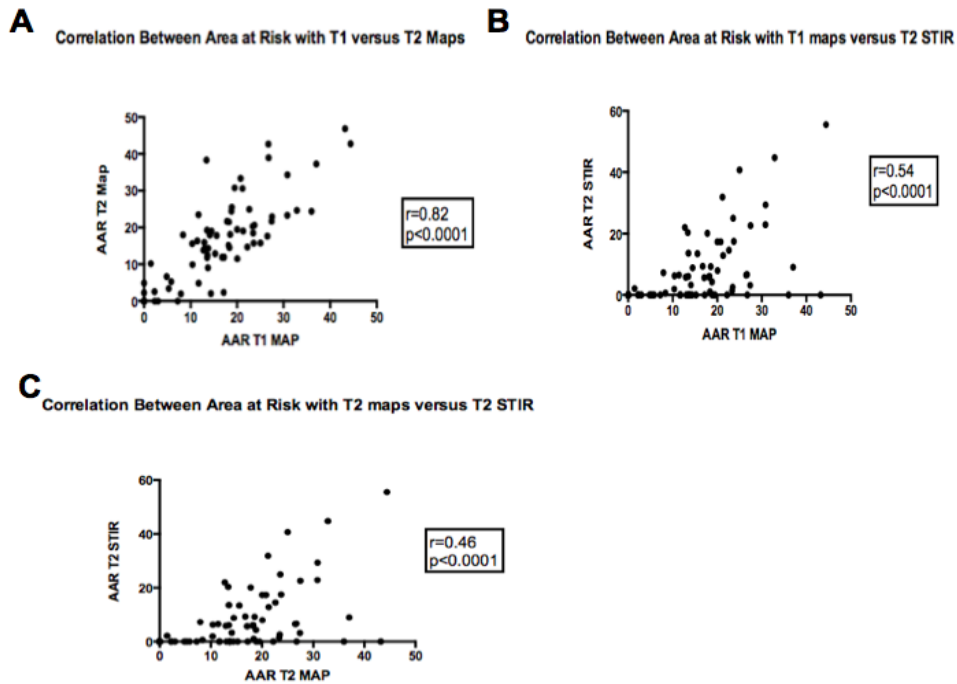
T1 maps more frequently reported evidence of regional myocardial edema (64 [88%] patients) when compared with T2 maps (63 [86%] patients), and T2W STIR (42 [58%] patients) (Table 11). For the comparisons of AAR with these methods, scatterplots of correlations are presented in Figure 26.

There was a good correlation between T1 and T2 maps for estimation of AAR ($r=0.82$, $P<0.001$; T1 vs. T2: $15.8\pm10.6\%$ of LV mass vs. $16.0\pm11.8\%$, $P=0.838$). The 95% limits of agreement for mean AAR estimated with T1 versus T2 maps were -13% and 13% of left ventricular mass with a minimal bias ($0.2\pm6.8\%$).

There were moderate correlations between AAR estimated with T1 maps versus T2W- STIR ($r=0.54$, $P<0.001$), and AAR estimated with T2 maps versus T2W-STIR ($r=0.46$, $P<0.001$). Mean AAR estimated with T2W STIR ($7.8\pm11.6\%$ of LV mass) was lower than that estimated with T1 ($P<0.001$) or T2 ($P<0.001$). The 95% limits of agreement for mean AAR estimated with T1 maps versus T2W- STIR and T2 maps versus T2W- STIR were wider with a higher level of bias when compared to the comparison for T1 vs. T2 maps (T1 versus T2W STIR -28% and 12% of LV mass, with a bias of $-8.0\pm10.6\%$; and for T2 versus T2 STIR maps -32% and 16%, with a bias of $-8.1\pm12.1\%$).

The average amount of myocardial salvage (%left ventricular myocardial mass) estimated with T1 maps ($10.1\pm8.9\%$) compared with T2 maps ($10.5\pm9.5\%$, $P=0.616$) was similar. However, the mean myocardial salvage estimated with T2W STIR ($4.7\pm9.7\%$ of left ventricular mass) was significantly lower than estimates with T1 ($P<0.001$) or T2 ($P<0.001$) maps.

Figure 26: Correlation between the area at risk estimated with T1 and T2 mapping and also dark blood T2W STIR imaging.



5.3.5 Diagnostic accuracy of T1, T2 maps and dark blood T2 STIR

The diagnostic accuracies of each edema imaging for identification of the infarct-related coronary artery, as defined by clinical data including the ECG and coronary angiogram are shown in table 11. The infarct-related artery was correctly identified more often with T2 maps when compared with other edema imaging methods (77% T2 maps, 71% T1 maps, 44% T2W STIR). However, when assessing diagnostic accuracy, there was no difference when comparing T1 and T2 maps ($P=0.125$). By contrast, a difference in diagnostic accuracy was shown between T1 maps and T2W- STIR ($P<0.001$), and T2 maps and T2W STIR ($P<0.001$). For infarct-related

artery identification, a high level of inter-observer agreement was found with T1 ($\kappa=0.790$, $P<0.001$) and T2 ($\kappa=0.794$, $P<0.001$) maps, while the level of agreement was moderate ($\kappa=0.555$, $P<0.001$) with T2W- STIR. Moreover, there was a lower level of discordance between observers for individual patients using T1 maps (discordant findings in 13.69%) and T2 maps (15.06%) respectively compared to dark blood T2W-STIR (30.14% cases, $p<0.001$).

5.3.6 Correlation of Area at Risk Estimated by T1 and T2 Weighted MRI Versus APPROACH lesion score

The mean APPROACH lesion score was 23.4 ± 12.6 of the left ventricular mass. Cardiac MRI estimates of area at risk did not correlate with the APPROACH lesion score. Area at risk: T1 vs. APPROACH ($r=0.13$, $p=0.29$), T2 vs. APPROACH ($r=0.11$, $p=0.37$), T2W STIR vs. APPROACH ($r=0.08$, $p=0.49$).

5.4 Discussion

The main results of our study are as follows. First, using 3.0 Tesla MRI, native T1 and T2 maps have a higher diagnostic accuracy compared to dark blood T2 STIR in detecting the infarct-related artery in patients with recent NSTEMI. Second, T1 and T2 maps produced highly congruent results when estimating the size of AAR and myocardial salvage. This was in contrast to dark blood T2 STIR imaging that tended to underestimate AAR and myocardial salvage. Third, there was a high level of inter-observer agreement for identification of the infarct-related artery with T1 and T2 maps, when compared to dark blood T2 STIR. Finally, artifacts were

significantly more prevalent with dark blood imaging when compared with T1 and T2 maps.

The detection of myocardial edema using a dark blood turbo spin-echo technique has been shown to facilitate prompt diagnosis of acute coronary syndromes and allow identification of both the area at risk and the amount of myocardial salvage post-reperfusion (39, 261, 262). Yet, despite great theoretical promise, the clinical reality of using dark blood T2-STIR imaging has been far from optimal due to methodological problems inherent with the technique. The limitations include data susceptibility to artifacts from respiratory and cardiac motion, the variability in myocardial signal related to surface coil intensity inhomogeneity, and the subjectivity of image interpretation (50, 51). Acute infarction alters T2 relaxation times by increasing myocardial cell water content (263) and transient ischaemia without infarction can also increase T2 time (39, 261, 264). Thus, a more reliable method of assessing the T2 signal alteration may increase the clinical utility of T2 edema imaging potentially leading to wider adoption. Recently, a non contrast, quantitative T2 mapping sequence using T2 SSFP has been proposed and been shown to be more accurate than conventional T2W STIR at predicting AAR in animal and human models (45, 54).

Previous experimental studies have also shown that T1 values increase with increasing myocardial water content and thus with ischaemia and infarction (45). By directly quantifying T1 values for each voxel in the myocardium, a parametric map can be generated representing the T1 relaxation times of any region of the heart. The most widely adopted T1-mapping sequence is based on the Modified Look- Locker Inversion-recovery (MOLLI) technique (55, 265). The use of T1 maps has also been shown to be more accurate at predicting edematous myocardium than dark blood T2W STIR(58). However, most of this work concerning the superior precision of T2

and T1 maps has been performed in the STEMI population, typically a syndrome associated with large degrees of myocardial injury.

5.4.1 Dark Blood Imaging

Following its development by Simonetti and colleagues Dark blood STIR edema imaging has enjoyed widespread use to assess for the presence of myocardial edema(49). Indeed several investigators have shown prognostic information using STIR imaging. For example, in a prospective study involving 88 patients with NSTEMI, Raman and colleagues highlighted the potential for T2STIR imaging in identifying edematous myocardium and to distinguish patients requiring coronary revascularization from those that did not. Moreover, the presence of edema was associated with a higher hazard of a cardiovascular event or death within 6 months after a non-ST elevation acute coronary syndrome.(37). However, the technical limitations of T2 weighted dark blood CMR have stimulated other groups to develop methods of edema imaging that are both quantitative and accurate.

Ferreira and colleagues investigated the diagnostic performance of dark blood imaging when compared to Bright Blood (ACUT2E) imaging as well as a novel T1 mapping method (ShMOLLI) in patients with Takotsubo cardiomyopathy and edema syndromes without infarction at 1.5 Tesla(58). The group demonstrated superior diagnostic accuracy with T1 mapping when compared to dark blood and bright blood T2 imaging methods. Verhaert and colleagues have also demonstrated superior accuracy of a novel T2 mapping technique when compared with dark blood imaging at 1.5 Tesla(54). Amongst 27 patients - only 11 of whom presented with NSTEMI, the use of T2 maps was associated with more reliable and improved

detection of edema.

NSTEMI is the commonest form of acute coronary syndrome and an important public health problem(23), yet information on the diagnostic and clinical utility of edema imaging with MRI in STEMI patients is lacking. To date, no study has directly compared T1 and T2 maps with dark blood T2W-STIR in NSTEMI. Our study has shown, for the first time in a large NSTEMI population, that at 3 Tesla, the diagnostic performance of dark blood imaging is inferior to newer novel mapping sequences with an underestimation of the AAR as well as myocardial salvage. The identification of edema and diagnostic accuracy of dark blood imaging was also limited which is important from a clinical perspective. Previous studies comparing dark blood imaging with newer T2 or T1 methods have included only small numbers of patients with NSTEMI. Overall the mean infarct size in these subpopulations have been moderate; 16.7% of LV mass reported by Payne et al (57) and in the study by Verhaert and colleagues the mean peak troponin concentration was 50mg/dl (54). In our NSTEMI population, the mean infarct size was 5.9% and troponin value was 0.92mg/dl - a much lower infarct size reflecting less myocardial injury. The poor performance of STIR in this population calls into question the use of dark blood edema MRI for imaging NSTEMI patients. This point becomes all the more relevant as the sensitivity of the biochemical detection of NSTEMI falls with the adoption of high sensitivity troponin assays. The higher sensitivity of T1 and T2 mapping for detecting subtle alterations in signal intensity that can occur in NSTEMI patients suggests that these methods may be more useful in clinical practice.

5.4.2 T1 and T2 Maps in NSTEMI

In-vivo and ex vivo studies have demonstrated that non-contrast T1 and T2 mapping can accurately quantify the ischaemic area at risk. STEMI is defined by acute coronary occlusion whereas the natural history of NSTEMI is different. In NSTEMI, thrombotic plaque rupture may lead to non-occlusive or intermittently lead to transient vessel occlusion. Both of these scenarios usually result in smaller degrees of myocardial injury, which may give rise to diagnostic uncertainty in clinical practice.

In a canine model of ischaemia and using a microsphere reference standard, Ugander and colleagues compared T1 (ShMOLLI) and T2 maps at 1.5 T for defining the area at risk. Both imaging modalities demonstrated equivalence with excellent correlation(45). Recently, Dall'Armellina and colleagues assessed T1 with T2 mapping amongst 41 patients presenting with myocardial infarction at 3 Tesla (48). 73% of the study cohort presented with STEMI. There was a similar diagnostic performance of T1 vs. T2 maps for detecting oedematous injured myocardium. In a subgroup analysis performed in only 9 patients with NSTEMI, the authors demonstrated a superior diagnostic performance of T1 maps over T2 maps and also less variability in T1 compared with T2 maps. In a much larger cohort of NSTEMI patients and using a different T1 mapping method, our results indicate that T1 and T2 maps had similar diagnostic accuracy for estimating the myocardial area at risk in patients with NSTEMI. In contrast to the findings of Dall'Armellina and colleagues although there was no advantage in terms of accuracy, there were significantly fewer artifacts with T2 maps compared to T1 maps suggesting an advantage for this mapping sequence. Importantly, and despite this lower degree of injury, the

utility of T1 and T2 mapping was preserved.

5.4.3 Angiographic Area at Risk

Several studies have clearly demonstrated the accuracy of both T1 and T2 maps in the assessment of the angiographic area-at-risk in patients with acute coronary syndromes. However, the patient populations have largely consisted of STEMI patients. The APPROACH score has been shown to correlate with the myocardium at risk derived through cardiac MRI (44), and the magnitude of the correlation increased with the transmural extent of infarction (59). Typically, NSTEMI patients have smaller, sub-endocardial infarcts and thus it is not surprising to find that the AAR as measured with oedema imaging sequences in our population did not correlate with the APPROACH score.

5.4.4 Clinical Application

Retrospective imaging of the ischaemic area at risk is clinically relevant since the amount of salvageable myocardium is a predictor of prognosis and the potential response to therapy(45).

This study demonstrates the greater accuracy of T1 and T2 maps at identifying oedematous myocardium when compared with T2W STIR imaging in patients with NSTEMI. Patients who experience a NSTEMI tend to be older, have more concomitant health problems, and multivessel coronary disease. Using a more sensitive marker of myocardial injury than dark blood T2W STIR in this heterogeneous population may allow for improved risk stratification for patients who would benefit from early invasive assessment and accurately identify the culprit territory

when faced with a patient who has multivessel coronary disease.

5.5 Study limitations

The timing of MRI post MI was influenced by the clinical course of the patients (e.g. recurrent ischaemia, the timing of invasive angiography etc.). Although, this variation in timing may have been introduced some measurement heterogeneity we think the MRI data became more representative of real life clinical practice. The participants were also enrolled in a clinical trial but the intervention in this trial was not relevant to the MRI study.

From an anatomical perspective, inter-individual variation in coronary artery distribution may confound infarct-artery assignment. In NSTEMI, multivessel coronary artery disease is common and there may be more than one culprit lesion. Therefore, it could be that an infarct-related artery which was missed on angiography was correctly identified with the MRI maps. Because patients underwent the cardiac MRI after invasive management with PCI, it is possible that the myocardial injury detected with T1, T2 and T2W STIR maps actually originated from the PCI treatment rather than the initial MI. However, according to the current Universal Definition of Myocardial Infarction(25) none of the participants in this study experienced peri-procedural MI.

5.6 Conclusion

T1 and T2 maps are novel, quantitative imaging methods that have a high diagnostic accuracy in detecting infarct-related artery in NSTEMI. They produce congruent results when estimating AAR, whereas using T2W STIR imaging yielded less accurate results with more artifact.

Findings suggest that T1 and T2 mapping represent a clinically valuable novel imaging method, with a particular usefulness in the assessment of reversible myocardial injury and salvaged myocardium. Based on our findings, the utility of T2W STIR imaging in the assessment of oedema in patients with NSTEMI is limited.

Chapter 7

Safety of Adenosine and Pressure Wires in Patients with Acute Coronary Syndromes

Summary

Background: Coronary guidewire-based diagnostic assessments with hyperaemia may cause iatrogenic complications. In 2013 the U.S. Food and Drug Administration (FDA) issued a safety warning on pharmacological stress testing. We assessed the safety of guidewire-based measurement of coronary physiology using intravenous adenosine in patients with an acute coronary syndrome.

Methods and Results: We prospectively enrolled invasively managed STEMI and NSTEMI patients in two simultaneously conducted studies in 6 centers. All of the participants underwent a diagnostic coronary guidewire study using intravenous adenosine (140 µg/kg/min) infusion for 1 - 2 minutes. 648 patients (n=298 STEMI patients in 1 hospital; mean time to reperfusion 253 min; n=350 NSTEMI in 6 hospitals; median time to angiography from index chest pain episode 3 (2, 5) days) were included between March 2011 to May 2013. Two NSTEMI patients (0.03% overall) experienced a coronary dissection related to the guidewire. No guidewire dissections occurred in the STEMI patients. The aortic systolic blood pressure was reduced during intravenous adenosine administration (systolic BP (rest vs. adenosine): 124.5 (26.0) mmHg vs. 111.7 (24.7) mmHg, (n=330) [95% CI 12.8 (11.3, 14.3) p<0.001]. Diastolic BP was also reduced (67.0 (12.8) mmHg vs. 60.5 (13.2) mmHg (n=330) [95% CI 6.5 (5.6, 7.4) p<0.001]. Chest symptoms were reported in the majority (86%) of patient's symptoms during the adenosine infusion. No serious adverse events occurred during infusion of adenosine and all of the symptoms resolved after the infusion ceased.

Conclusion: In this multicenter analysis, guidewire-based measurement of FFR using intravenous adenosine was safe in patients following STEMI or NSTEMI.

6.1 Introduction

Coronary guidewire-based sensors can be used in the cardiac catheterization laboratory to provide functional information on coronary artery disease severity and microvascular function. The myocardial fractional flow reserve (FFR) assesses the physiological significance of a coronary stenosis and is expressed as the ratio of maximal blood flow in a stenotic artery to maximal flow if theoretically the artery was unobstructed. FFR-guided management is evidence-based in patients with stable coronary artery disease (DEFER(228), FAME(119), FAME-2(229)) and has emerging clinical utility for measurement of non-infarct artery disease in patients with recent or acute myocardial infarction (MI)(126). However since FFR measurement involves pharmacological hyperaemia and guidewire instrumentation, there are theoretical risks of serious adverse events (SAE) including ventricular arrhythmias with intravenous adenosine and coronary dissection (both ~0.5% incidence)(230).

Intravenous adenosine induces hyperaemia through interactions with A2A receptors. However, due to the ubiquitous expression of adenosine receptors, adenosine is also associated with unwanted off-target side-effects. For example, interaction with bronchial A2B receptors can lead to mast cell degranulation and bronchoconstriction(147). Furthermore, activation of cardiac A1 receptors has a myocardial depressant effect with negative chronotropic and dromotropic effects(267). It is these unwanted effects of adenosine that have motivated researchers to find other drugs for initiation of hyperaemia or develop non hyperaemic indices of stenosis assessment in the catheter laboratory(217, 268).

Intracoronary adenosine may also be used therapeutically for the treatment of no-reflow in STEMI(89), and the role of FFR-guided PCI in STEMI patients with multivessel coronary

disease is currently being evaluated in the COMPARE-ACUTE (NCT01399736), COMPLETE (NCT01740479) and PRIMULTI (NCT01960933) clinical trials.

In November 2013 the United States (US) Food and Drug Administration (FDA) issued a safety announcement on the risk of myocardial infarction (MI) and death in patients receiving Adenoscan (adenosine) for stress testing(269). This announcement followed from reports in the FDA Adverse Event Reporting System (FAERS) and medical literature of serious adverse events (SAE) from 1995 to 2013, including 6 cases of MI and 27 cases of death following adenosine administration (typically within 6 hours) (269).

We aimed to prospectively assess the safety of guidewire-based measurement of coronary physiology using intravenous adenosine amongst patients with acute or recent myocardial infarction (MI). Based on our prior experience with intravenous adenosine in this setting (129, 266), we hypothesised that in accordance with recent literature, intravenous adenosine would be safe and well tolerated (270).

6.2 Methods

6.2.1 Study Population

We simultaneously conducted two prospective studies involving assessments of coronary physiology in patients with acute or recent MI. Two hundred and ninety-eight STEMI patients were enrolled acutely and had coronary physiology measured invasively in the culprit coronary artery with a diagnostic coronary guidewire (PressureWire Certus™, St Jude Medical) during primary or rescue PCI. The protocol did not involve FFR measurements in the non-infarct arteries. The enrolment period was March 2011 - November 2012. Patients diagnosed with an acute STEMI and who were undergoing primary or rescue PCI were eligible to participate. In the second study, three hundred and fifty NSTEMI patients were enrolled from six hospitals in the United Kingdom participated (3 academic and 3 non-academic regional hospitals). The patients in this study underwent urgent invasive management and had an FFR measurement in one or more coronary arteries with at least a single coronary stenosis $\geq 30\%$ severity of the reference vessel diameter by visual assessment. The patients with NSTEMI were enrolled during urgent care and the median time to invasive angiography was 3 days.

The exclusion criteria for administration of intravenous adenosine included evidence of 2nd or 3rd degree heart block on the ECG, long QT syndrome, cardiogenic shock, or a history of asthma concurrently treated with bronchodilators. The exclusion criteria for both studies are provided in Tables 12 and 13. The study was approved by the UK National Research Ethics Service and all participants provided written informed consent.

Table 12

STEMI Study Exclusion Criteria
2 nd or 3 rd degree heart block on ECG
Long QT syndrome
Cardiogenic shock
History of asthma concurrently treated with bronchodilators
Terminal systemic illness (e.g. cancer limiting survival <12 months)
Pregnancy
Inability to provide informed consent

Table 13

NSTEMI Exclusion Criteria
Contra-indications to intravenous adenosine including 1) A history of asthma concurrently treated with bronchodilators; 2) 2 nd or 3 rd degree heart block on ECG; 3) Long QT syndrome
A life expectancy < 1 year (e.g. cancer limiting survival <12 months)
Pregnancy
Inability to provide informed consent
Hemodynamic Instability
MI with persistent ST elevation
Ineligible for coronary revascularization on clinical grounds
Plan for non-coronary heart surgery
Prior CABG
Angiographic evidence of severe (e.g. diffuse calcification) or mild (< 30% severity) coronary disease
Intolerance to anti-platelet drugs,

6.3 Catheter laboratory management

The clinical and catheter laboratory management followed contemporary guidelines for STEMI and NSTEMI(23).

6.3.1 Measurement of FFR

Figure 27- Example of Haemodynamic Recording



A hemodynamic recording obtained from a diagnostic pressure- and temperature-sensitive guidewire (PressureWire Certus™, St. Jude Medical, Mn.) located in a culprit coronary artery at the end of primary PCI.

The blue arrow represents the thermodilution recordings during resting conditions before adenosine administration. The thermodilution curve represents the transit time for the change in

temperature detected by the distal guidewire thermistor following intra-coronary bolus injection of saline (room temperature) via the guiding catheter. The subsequent yellow arrow represents the transit times for thermodilution curves following intra-coronary injections of saline during hyperaemia with adenosine (140 µg/kg/min). During hyperaemia, there is evidence of a reduction in arterial blood pressure depicted by the yellow arrow, reflecting the typical hemodynamic response in the systemic and coronary circulations to intravenous adenosine.

In patients with STEMI, infarct artery coronary physiology (FFR) was measured at the end of the primary or rescue PCI (Figure 1). In patients with NSTEMI, FFR was measured at the beginning of the diagnostic procedure in all participants. Intravenous adenosine was administered at a rate of 140 µg/kg/min via a large peripheral vein for 1 - 2 minutes. (Table 24).

Table 14 – Methods for Making Adenosine Infusion

Step	Action
1.	Remove 40ml from a 100ml bag of IV saline and discard
2.	Draw up 30ml (90mg) of adenosine (3mg/ml either 15x2ml vials or 3x10ml vials)
3.	Add adenosine to the 60 ml IV saline giving a concentration of 1mg/ml

The patient's response to adenosine administration was a pre-defined safety outcome. Aortic and distal coronary pressures were recorded invasively before and during adenosine administration. In addition, patients' symptoms and heart rate during the adenosine infusion were also prospectively documented using a study proforma. All SAEs in study participants were prospectively documented by clinical and research staff after the patient was enrolled in the

study in line the trial protocol. All adverse events were recorded in the clinical report form (CRF). SAEs were notified to the Sponsor of the studies for pharmacovigilance and assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004.

An SAE was defined as an event that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is otherwise considered medically significant by the investigator.

Major adverse cardiac events (MACE), were defined as the occurrence of death, myocardial infarction, or hospitalisation for heart failure(271). In the STEMI study, source data for all of the SAE and MACE were assessed by a cardiologist who was independent of the research team. This cardiologist was blinded to all of the other clinical data. In the NSTEMI study, source clinical data for all SAE of suspected cardiovascular origin and all deaths were reviewed by an independent clinical event committee blinded to treatment group assignment (FFR-guided group or angiography guided group). The CEC also assessed the angiograms of SAE attributed to procedure-related complications.

6.4 Statistics

Continuous data with a normal distribution were summarized with the mean \pm standard deviation (SD). Paired t-tests were used to assess hemodynamic data before and during adenosine administration. Significance was defined as a p value < 0.05 . The statistical analyses were performed using the SPSS statistical software package 14.0 for Windows (SPSS Inc., Chicago, IL, USA).

6.5 Results

Baseline characteristics

648 patients (n=298 patients with STEMI in 1 hospital; n=350 patients with NSTEMI in 6 hospitals) were included between March 2011 - May 2013. Their clinical characteristics are presented in Table 15.

In the patients with STEMI, evidence of haemodynamic instability on arrival in the cardiac catheter laboratory was common. Thirty-three (11.1%) patients had a systolic blood pressure (BP) of < 90 mmHg, 20 (7.2%) patients had ventricular fibrillation (VF) or ventricular tachycardia (VT) before or during PCI but prior to adenosine administration, and 4 (1.4%) patients received intra-aortic balloon pump (IABP) counterpulsation therapy during the PCI. In the patients with NSTEMI there were no patients with VF/VT during the procedure and only 1 (0.3%) patient required IABP.

Table 15 – Baseline Clinical Characteristics

Characteristics*	STEMI patients n=298	NSTEMI patients n=350
Clinical		
Age, years	59.4	62.0
Male sex, n (%)	216 (72)	260 (74)
BMI, (kg/m ²)	28.7	29 (5)
History		
Hypertension, n (%)	95 (32)	159 (45)
Current smoking, n (%)	184 (62)	143 (41)
Hypercholesterolemia, n (%)	81 (27)	127 (36)
Diabetes mellitus‡, n (%)	32 (11)	52 (15)
Previous myocardial infarction, n (%)	20 (7)	46 (13)
Previous PCI, n (%)	16 (5)	38 (11)
Presenting characteristics		
Heart rate, bpm	80 (44)	74 (16)
Systolic blood pressure, mmHg	135 (25)	141 (27)
Diastolic blood pressure, mmHg	79 (14)	81 (17)
Time from symptom onset to reperfusion, min	253	-
Time from index episode of myocardial ischemia to invasive angiogram, days	-	3 (2, 5)
Ventricular tachycardia or fibrillation†, n (%)	20 (7)	0 (0)
Heart failure, Killip class at presentation, n (%)		
I	212 (71)	308 (88)
II	64 (22)	33 (9)
III	16 (5)	5 (2)
IV	6 (2)	4 (1)
Coronary angiography		
Reperfusion strategy, n (%)		
Primary PCI	275 (92)	-
Rescue PCI (failed thrombolysis)	23 (8)	-
Adjunctive Therapy During PCI		
Aspirin (%)	297 (99)	348 (99)
Clopidogrel (600mg) (%)	297 (99)	337 (96)
Heparin (%)	298 (100)	333 (95)

Anti-GP IIb/IIIa (%)		273 (92)	79 (26)
Number of diseased arteries, n (%)	0	0 (0)	10 (3)
	1	165 (55)	130 (37)
	2	95 (32)	141 (40)
	3	38 (13)	60 (17)
	4	0 (0)	9 (3)
Culprit artery, n (%)	LMS	0 (0)	2 (1)
	LAD	110 (37)	152 (43)
	LCX	55 (18)	106 (30)
	RCA	133 (45)	90 (26)
TIMI coronary flow grade pre-PCI, n (%)	0/1	214 (72)	-
	2	56 (19)	-
	3	28 (9)	-
TIMI coronary flow grade post-PCI, n (%)	0/1	2 (1)	33 (9)
	2	14 (5)	27 (8)
	3	282 (94)	289 (83)

6.5.1 Symptoms and adverse events

During adenosine infusion, 255 (85.6%) STEMI patients reported symptoms including chest discomfort, dyspnoea and facial flushing, all of which resolved immediately after the infusion ceased. There were no other symptoms reported. No MACE or atrial or ventricular arrhythmias occurred in association with intravenous adenosine administration. There were no SAEs related to adenosine.

In the STEMI cohort, MACE occurred in 3 (1.0%) patients within 24 hours of the PCI. One patient experienced an acute stent thrombosis associated with a dissection at the distal end of the stent; one patient with severe left ventricular dysfunction experienced ventricular fibrillation in the coronary care unit; one patient died suddenly from myocardial rupture that was confirmed at autopsy. All of these events occurred in the coronary care unit and none of these events were

temporally associated with the adenosine infusion in the catheter laboratory. In the STEMI cohort there were no pressure-wire related dissections and no SAE related to arrhythmias.

In the NSTEMI cohort, no MACE occurred in association with the adenosine infusion. There were 2 (0.6%) cases of coronary dissection related to the guidewire. There were 4 cases of in-hospital adverse events, including 3 (0.9%) cases of contrast nephropathy and 3 (0.9%) cases of major bleeding but none related to adenosine infusion. There were no SAE related to bradyarrhythmias or tachyarrhythmias and FFR was measured in all subjects.

6.5.2 Haemodynamic changes

All Patients

In 330 patients with complete hemodynamic data (n=186 STEMI, n=144 NSTEMI), aortic systolic blood pressure was reduced during adenosine administration (systolic BP (rest vs. adenosine): 124.5 (26.0) mmHg vs. 111.7 (24.7) mmHg, (n=330) [95% CI 12.8 (11.3, 14.3) p<0.001] as was diastolic BP (67.0 (12.8) mmHg vs. 60.5 (13.2) mmHg (n=330) [95% CI 6.5 (5.6, 7.4) p<0.001]. Heart rate increased to 64.7 (13.0) bpm from 58.3 (12.1) bpm, [95% CI 6.3 (5.6, 7.1) p<0.001]. The proximal aortic pressure (Pa) was also reduced during adenosine administration (systolic BP (rest vs. adenosine): 119.7 (26.6) mmHg vs. 104.2 (25.0) mmHg, (n=351) [95% CI 15.5 (13.9, 17.0) p<0.001] as was the distal coronary pressure (64.7 (14.4) mmHg vs. 55.2 (14.4) mmHg [95% CI 9.4 (8.5, 10.4) p<0.001].

STEMI

Table 16: Blood pressure and heart rate at the start and end of emergency PCI in 298 STEMI subjects.

Parameter	PCI start	PCI end	Mean Change (CI)	P value
Mean heart rate (SD) bpm	80.1 (44.1)	79.5 (14.5)	0.6 (-4.3, 5.6)	0.800
Mean systolic BP (SD) mmHg	135.1 (24.7)	121.0 (21.1)*	14.0 (11.6, 16.4)	<0.001
Mean diastolic BP (SD) mmHg	79.0 (13.9)	71.9 (12.9)*	7.0 (5.6, 8.5)	<0.001

Table 17: Coronary (Pd) systolic and diastolic blood pressure recorded in 258 STEMI subjects.

Blood Pressure (BP)	Rest	Adenosine	Mean Change (CI)	P value
Mean systolic (SD) mmHg	114.6 (22.6)	98.8 (21.8)*	15.8 (14.1, 17.5)	<0.001
Mean diastolic (SD) mmHg	65.5 (13.9)	56.1 (14.4)*	9.4 (8.4, 10.3)	<0.001

In the STEMI cohort (n=298), non-invasive hemodynamic data were available for all of the participants (Table 16). Distal coronary (Pd) artery blood pressure was recorded in 258 STEMI subjects (Table 17) and complete intracoronary hemodynamic data before and during adenosine infusion were available in 186 STEMI patients. The mean (SD) aortic systolic BP fell from 120.0 (22.6) mmHg at baseline to 106.5 (21.3) mmHg during adenosine infusion [95% CI 13.5 (11.6, 15.5) p<0.001]. Aortic diastolic BP was also reduced by adenosine infusion (67.9 (13.5) mmHg vs. 61.0 (13.6) mmHg [95% CI 7.0 (5.8, 8.1) p<0.001] whereas heart rate increased from

63.2 (12.1) bpm at rest to 69.8 (12.5) bpm [95% CI 6.6 (5.6, 7.6) $p<0.001$]. Compared to patients who did not experience symptoms with adenosine, patients who did experience symptoms had a greater rise in heart rate, but BP changes were similar (Table 18).

Table 18: Blood pressure and heart rate of STEMI patients with symptoms recorded (n=186) and who reported symptoms vs. no symptoms.

Parameter	Symptoms (n=154)	No Symptoms (n=32)	Mean Difference (CI)	P value
Mean (SD) systolic change, mmHg	-14.2 (13.5)	-10.5 (13.5)	-3.6 (-8.3, 1.5)	0.167
Mean (SD) diastolic change, mmHg	-7.2 (7.8)	-6.0 (8.4)	-1.2 (-4.2, 1.9)	0.451
Mean (SD) HR change, bpm	7.1 (7.0)	4.0 (6.2)*	3.1 (0.5, 5.7)	0.020

NSTEMI

In the NSTEMI cohort (n=350), complete non-invasive aortic hemodynamic data and distal coronary (Pd) hemodynamic recordings were available for 144 and 165 patients respectively. The mean (SD) non-invasive aortic systolic BP reduced from 130.3 (28.8) mmHg under resting conditions to 118.5 (27.0) mmHg during adenosine infusion [95% CI 11.8 (9.4, 14.2) $p<0.001$]. Aortic diastolic BP was also reduced by adenosine infusion (65.9 (11.9) mmHg vs. 60.0 (12.7) mmHg [95% CI 5.9 (4.5, 7.2) $p<0.001$]. Heart rate increased to 58.1 (11.0) bpm from 52.1 (8.8)

bpm (n=144) [95% CI 6.0 (4.8, 7.2) p<0.001] and distal coronary (Pd) pressure was reduced also (Table 19).

Table 19. Distal coronary (Pd) artery blood pressure recorded in 165 NSTEMI subjects.

Abbreviations – Blood Pressure (BP), Standard Deviation (SD) *p<0.001 vs. baseline (paired t-test)

Blood Pressure (BP)	Rest	Adenosine	Mean Change (CI)	P value
Mean systolic (SD) mmHg	125.7 (28.3)	110.4 (26.4)*	15.3 (13.0, 17.7)	<0.001
Mean diastolic (SD) mmHg	63.7 (14.2)	53.7 (13.7)*	10.0 (8.4, 11.5)	<0.001

6.6 Discussion

We report the largest study to date of guidewire-based measurements of FFR in patients with acute coronary syndromes. Our study is the first to report information on a pre-specified outcome relating to the safety of intravenous adenosine in patients with an acute STEMI or recent NSTEMI, who were prospectively enrolled simultaneously in parallel studies.

The main findings of our multicenter study are that, first, coronary dissection due to the guidewire was rare ($\leq 0.03\%$). Second, brief intravenous adenosine infusion in MI patients for diagnostic purposes was commonly associated with symptoms but these symptoms were brief

and self-limiting and were not associated with any SAEs; most importantly, the use of adenosine was safe and not associated with any SAEs during routine emergency care.

Only 2 guidewire-related coronary dissections occurred in 698 prospectively enrolled MI patients undergoing emergency or urgent invasive management. This result represents evidence for the safety of guidewire-based assessments of coronary physiology. Guidewire dissections were less common than in previous studies [e.g. RIPCORD (1.5%)](230). We think that the timing of the pressure wire study within the procedure partially explains the difference in the dissection rates. In the patients with acute STEMI, pressure wire instrumentation in the infarct-artery post-PCI was not associated with any complications. In the patients with recent NSTEMI, the 2-guidewire dissections occurred in diagnostic procedures before stent implantation. In the 350 NSTEMI participants in this trial, 706 lesions ($\geq 30\%$ lumen narrowing) were reported and FFR data were obtained in 704 ($>99\%$) of these lesions. On average 2 arteries per patient were instrumented with a pressure wire. Despite this, the incidence of guidewire dissections in the NSTEMI patients was very low and this experience is evidence of safety in the hands of trained cardiologists.

In our study, predictable symptoms associated with adenosine occurred in the majority of patients and can be explained by the pharmacological effects of this naturally occurring vasodilator(270). However, since the half life of adenosine is < 10 seconds, these symptoms are extremely short-lived(272). Patients who experienced symptoms had a slightly higher increase in heart rate. A minority of patients (14%) did not experience symptoms with adenosine infusion. This may be explained by the presence of concurrent chest symptoms associated with myocardial infarction and also treatment with sedative and opiate therapies. There were no serious adverse events associated with intravenous adenosine. None of the patients experienced sustained atrial

or ventricular tachyarrhythmia. Overall, the reported symptoms that were observed in these cohorts were typical of what might be expected with intravenous adenosine. Based on the evidence of safety in this study, we think that when a clinician plans to administer intravenous adenosine, the patient should be advised that symptoms are likely but self-limiting and not associated with any other consequences. Adverse events, such as atrial and ventricular fibrillation, are rare and, in fact, no such events occurred in the 648 MI patients in this analysis.

Systolic and diastolic blood pressures were reduced with intravenous adenosine consistent with an A2A receptor-mediated response. However, a rise in heart rate of >10% or a fall in systolic BP >10% occurred in less than half of the STEMI and NSTEMI patients in our study. These observations could be explained by the fact that the patients already had tachycardia due to STEMI, and they had been treated with vasoactive drugs, which attenuate the systemic reflex sympatho-excitation response (e.g. intravenous morphine). It is also possible that there was an attenuated sympathetic response due to beta blocker treatment.

Of the 6 hospitals in the NSTEMI cohort 3 were regional non-academic centers without a track record in coronary physiology research. The multicenter design was intended to make the results of this trial more representative of routine care, relevant to “real world” practice and novel.

Potential diagnostic applications are emerging for FFR to inform the acute treatment decisions for patients with non-infarct artery disease(131). Intracoronary adenosine is used to treat no-reflow and FFR-guided PCI in STEMI patients with multivessel coronary disease, is currently being evaluated in the COMPARE-ACUTE (NCT01399736), COMPLETE (NCT01740479) and PRIMULTI (NCT01960933) trials.

Adenosine is an established drug for use in pharmacological stress testing. Adenoscan has been marketed from 18 May 1995. From this date until 10 April 2013 the FAERS database accrued

26 reports of myocardial infarction (MI) and 29 deaths with regadenoson and 6 reports of myocardial infarction and 27 deaths reported with Adenoscan. There were two case reports of MI associated with Lexiscan administration but none with Adenoscan(274, 275) and the incidence of cardiovascular adverse events associated with these drugs is similarly uncommon(198, 215). In light of these post-marketing reports the FDA recommended to *"Avoid using these drugs (Lexiscan or Adenoscan) in patients with signs or symptoms of unstable angina or cardiovascular instability, as these patients may be at greater risk for serious cardiovascular adverse reactions"*(269).The FDA warning was directed to office-based administration of intravenous adenosine, and this environment contrasts with the cardiac catheterization laboratory where medical support is immediately available to treat patients with iatrogenic complications. Our results also provide reassurance for the use of intravenous adenosine in the catheter laboratory setting.

In contrast to the FDA recommendations, our findings are supported by the results from similar studies in other centers, in which intravenous adenosine has been used in patients with acute MI(180, 243, 276). Moreover, a meta-analysis evaluating the safety and efficacy of intracoronary adenosine in 460 patients with STEMI undergoing PCI found no difference in the safety endpoints of bradycardia, ventricular arrhythmia and chest pain compared with placebo(277). Our study is different since the safety of diagnostic guidewire instrumentation and systemic administration of adenosine (rather than intracoronary adenosine) were prospectively assessed in NSTEMI and STEMI patients. Another study, using a similar protocol for adenosine, demonstrated all patients tolerated adenosine infusion with no episodes of clinically significant bradycardia(243). In our hands, adenosine was not associated with any SAE when administered

to reperfused patients with STEMI at the end of emergency PCI for a short period of time (1-2 minutes) and the absence of SAE in the NSTEMI patients provides further evidence of safety.

6.7 Limitations

Our study has several limitations. First, we do not have information on other hyperaemic drugs, such as regadenoson. Second, although safety assessments were performed and recorded in all of the patients at the time of the procedure, symptom reporting was incomplete. The available results confirm that symptoms typically occur with intravenous adenosine. Lastly pressure wire studies were restricted to the infarct-related artery rather than the non-infarct artery in the STEMI cohort study. Nonetheless, we provide comprehensive hemodynamic data and information on symptoms from prospective evaluations in individual patients who were enrolled in studies that had been designed with an open approach to enrolment of ‘all-comers’. We think our observations are representative of ‘real-world’ clinical practice.

6.8 Conclusion

Guidewire-based measurement of coronary physiology involving intravenous adenosine infusion was safe during emergency or urgent PCI for STEMI and NSTEMI. The symptoms related to adenosine were predictable, self-limiting and not associated with adverse events.

Future Directions

This thesis has examined a variety of invasive and non-invasive methods for evaluating patients with acute coronary syndromes. However, there are many emerging techniques that are being evaluated at the time of writing this thesis that may also assist in the assessment of patients with NSTEMI.

The Instantaneous Wave Free Ratio (iFR)

The instantaneous wave free ratio is a novel method of assessing coronary stenoses in patients undergoing coronary angiography. It is an adenosine free index and assumes that at a specific point in diastole there exists a period of minimal resistance. This is known as a 'wave free period'.⁽²⁷⁸⁾ In theory, as resistance is minimised there is no need to use adenosine to achieve hyperaemia thus avoiding potentially unwanted pharmacological effects. Presently, there is a paucity of outcome data with this technique and in particular in patients with ACS. However, its potential to assist with revascularisation decisions amongst patients with NSTEMI will be an exciting area of future research.

Optical Coherence Tomography (OCT)

Optical coherence tomography is an optical analogue of ultrasound using light rather than sound to produce an image. As distinct from sound, it has a ten times higher resolution (15 microns) meaning that highly detailed imaging can be achieved. For many years, OCT has been implemented in the characterisation of the retina. However, it was not until 1996 that OCT was

used in coronary arteries to characterise plaque. Unlike traditional intracoronary imaging techniques, OCT has a ten-fold higher resolution thereby providing a more definitive anatomical assessment within the vessel. This advantage has seen OCT successfully applied to the assessment of atherosclerotic plaque, stent apposition and coverage(279).

The best histological precursor for a ruptured plaque, which is the cause of 80% of MI, is the so-called thin fibrous cap atheroma (TCFA). The in-vivo visualization of a thin fibrous cap cannot be appreciated by coronary angiography and similarly, is also poorly detected by Intravascular Ultrasound. With its excellent spatial resolution, OCT is ideally placed to identify vulnerable plaque that could result in ACS. Recent studies have demonstrated clinical benefit in pacifying these “hot” atherosclerotic plaques which were once thought to remain dormant.(87, 280) The use of OCT to identify and then treat these ‘hot plaques’ is currently under investigation in clinical trials and represents an innovative and exciting area of ongoing research in patients with ACS.

CT Coronary Angiography.

A number of CT-based coronary plaque characteristics of a “vulnerable plaque” associated with culprit lesions for future ACS have been identified in retrospective observational studies

Non Calcified Plaque, spotty calcification, higher mean plaque volume and positive remodelling are all features associated with a high positive and high negative predictive value for future ACS. Furthermore, it has been proposed that the presence of a ring-like attenuation in a CT angiographic cross section may be a surrogate marker of TCFAs(281).

The use of these high risk plaque features together with novel techniques that assess functional significance such as CT-FFR and stress perfusion CT offer an exciting opportunity in future noninvasive ACS research.

Conclusion

In conclusion we have shown that the use of fractional flow reserve (FFR) is feasible amongst patients with NSTEMI and has clinical utility. The increase in prescription of medical therapy in the FFR guided arm was an important landmark for the study as was the demonstration of discordance between the interpretation of the angiogram and FFR. However, as this was a pilot study it will not be a practice changing trial. The increase in late events in the FFR guided arm is also of interest. Due to the lack of power of the study any inferences regarding the use of FFR in NSTEMI cannot be made. Rather, this study provides valuable data to inform a larger, multinational trial that has sufficient power to answer the important question regarding the use of FFR in NSTEMI.

Another important finding of this study was concerning the validity of FFR thresholds for ischaemia in NSTEMI. This is a controversial area of interventional cardiology that we have successfully answered. We have clearly shown that amongst patients with NSTEMI, the current threshold of FFR (≤ 0.8) was diagnostic of inducible perfusion defects when compared to a non-invasive gold standard (Stress perfusion CMR) with a high level of accuracy. This provides more evidence in support of using FFR routinely amongst patients with NSTEMI.

We have also shown that traditional oedema imaging techniques (dark blood T2W) are inferior to newer, novel mapping methods (T1 and T2) for the estimation of the area at risk and myocardial salvage. This has important implications for the use of such techniques amongst patients with NSTEMI. Myocardial salvage is an increasingly important end point in many clinical trials. Since dark blood imaging failed to detect oedema and underestimated salvage in a significant proportion of patients, when compared to both T1 and T2 maps, its use as an oedema imaging method in NSTEMI should be questioned.

Finally, we have confirmed the safety of using adenosine in patients with ACS in a large cohort of both STEMI and NSTEMI. This has important implications in light of the recent FDA announcement.

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